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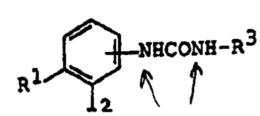
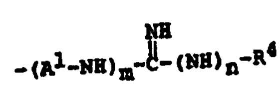
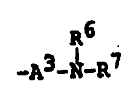
(54) Title: **UREA DERIVATIVES AS 5-HT ANTAGONISTS**

(57) Abstract

A compound of formula (I) wherein R^1 is cyano, thiocarbamoyl, a group of formula (a) in which R^4 is hydrogen, lower alkyl which may have optionally substituted aryl, acyl, optionally substituted aryl, lower alkylthio or 1-lower alkylindolyl, A^1 is lower alkylene, and m and n are each 0 or 1, a group of the formula $-A^2-R^5$ in which R^5 is morpholino, piperidino, 4-arylpiperazin-1-yl, phthalimido, 1,2,3,4-tetrahydroquinolin-1-yl, 1,2,3,4-tetrahydroisoquinolin-2-yl or imidazol-1-yl, and A^2 is lower alkylene, or a group of formula (b) in which R^6 and R^7 are each hydrogen, optionally substituted aryl, acyl, pyridyl(lower)alkyl, thienyl(lower)alkyl, 3,4-dihydroisoquinolinyl, (lower alkylimino) (optionally substituted aryl) methyl or lower alkyl which may have optionally substituted aryl, and A^3 is lower alkylene, and R^2 is hydrogen; or R^1 and R^2 are linked together to form (1), (2), or (3), in which R^8 is amino or acylamino, and R^9 is hydrogen, acyl or lower alkyl which may have optionally substituted aryl, and R^3 is 1-lower alkylindolyl, benzofuranyl, dihydrobenzofuranyl, or optionally substituted aryl, and a pharmaceutically acceptable salt thereof, which is useful as a medicament for prophylactic and therapeutic treatment of 5-HT mediated diseases.


(I)


(a)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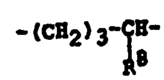
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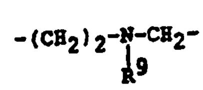
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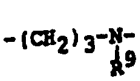
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DESCRIPTION

UREA DERIVATIVES AS 5-HT ANTAGONISTS

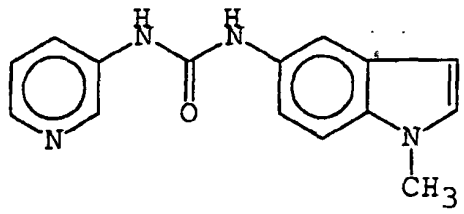
TECHNICAL FIELD

The present invention relates to novel urea derivatives and a pharmaceutically acceptable salt thereof. More particularly, it relates to novel urea derivatives and a pharmaceutically acceptable salt thereof which have pharmacological activities such as 5-hydroxytryptamine (5-HT) antagonism and the like.

Said urea derivatives or a pharmaceutically acceptable salt thereof are useful as a 5-HT antagonist for treating or preventing central nervous system (CNS) disorders such as anxiety, depression, obsessive compulsive disorders, migraine, anorexia, Alzheimer's disease, sleep disorders, bulimia, panic attacks, withdrawal from drug abuse such as cocaine, ethanol, nicotine and benzodiazepines, schizophrenia, and also disorders associated with spinal trauma and/or head injury such as hydrocephalus, and the like in human being or animals.

BACKGROUND ART

With regard to the states of the arts in this field, for example, the following compound is known.



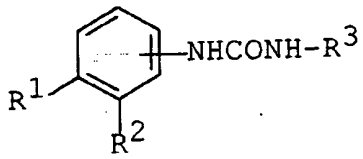
(A)

(WO 93/18026)

DISCLOSURE OF INVENTION

As a result of an extensive study, the inventors of the present invention could obtain the urea derivatives which have strong pharmacological activities.

The urea derivatives of the present invention are novel and can be represented by the formula (I) :



(I)

wherein R^1 is cyano, thiocarbamoyl,

a group of the formula :

$$-(A^1\text{-}NH)_m\text{-}\overset{\overset{NH}{\|}}{C}\text{-}(NH)_n\text{-}R^4$$

in which R^4 is hydrogen, lower alkyl which may have optionally substituted aryl, acyl, optionally substituted aryl, lower alkylthio or 1-lower alkylindolyl,

A^1 is lower alkylene, and

m and n are each 0 or 1,

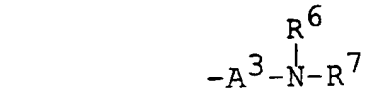
a group of the formula :

$$-A^2\text{-}R^5$$

in which R^5 is morpholino, piperidino, 4-arylpiperazin-1-yl, phthalimido, 1,2,3,4-tetrahydroquinolin-1-yl, 1,2,3,4-tetrahydroisoquinolin-2-yl or imidazol-1-yl, and

A^2 is lower alkylene, or

a group of the formula :

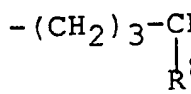


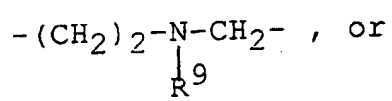
in which R^6 and R^7 are each hydrogen, optionally substituted aryl, acyl, pyridyl(lower)alkyl, thienyl(lower)alkyl, 3,4-dihydroisoquinolinyl, (lower alkylimino)(optionally substituted aryl)methyl or lower alkyl which may have optionally substituted aryl, and

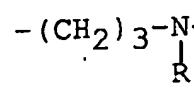
A^3 is lower alkylene, and

R^2 is hydrogen; or

R^1 and R^2 are linked together to form







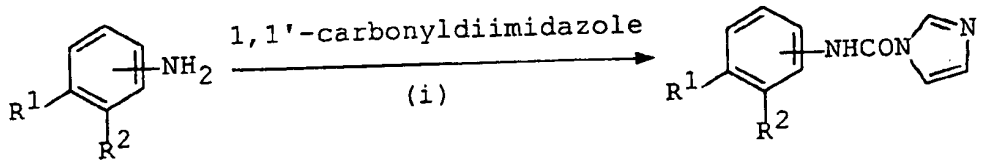
in which R^8 is amino or acylamino, and

R^9 is hydrogen, acyl or lower alkyl which may have optionally substituted aryl, and

R^3 is 1-lower alkylindolyl, benzofuranyl, dihydrobenzofuranyl, or optionally substituted aryl.

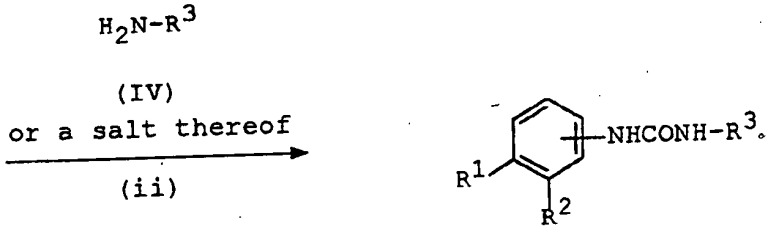
According to the present invention, the object compounds (I) can be prepared by the following main processes :

Process 1



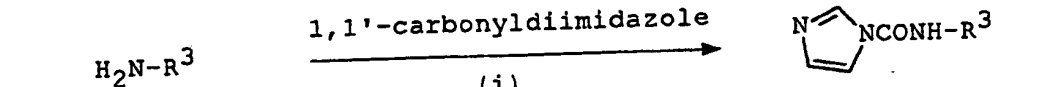
(II)
or a salt thereof

(III)
or a salt thereof

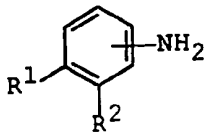


(I)
or a salt thereof

Process 2

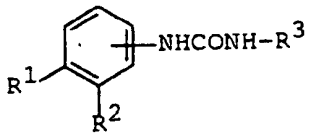


(V)
or a salt thereof



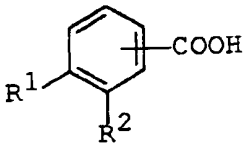
(II)
or a salt thereof

(ii)



(I)
or a salt thereof

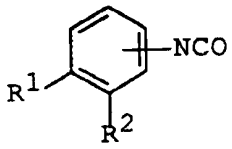
Process 3



(VI)
or a salt thereof

Curtius Rearrangement

(i)

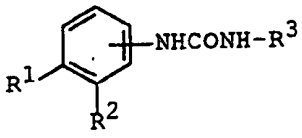


(VII)
or a salt thereof

H_2N-R^3

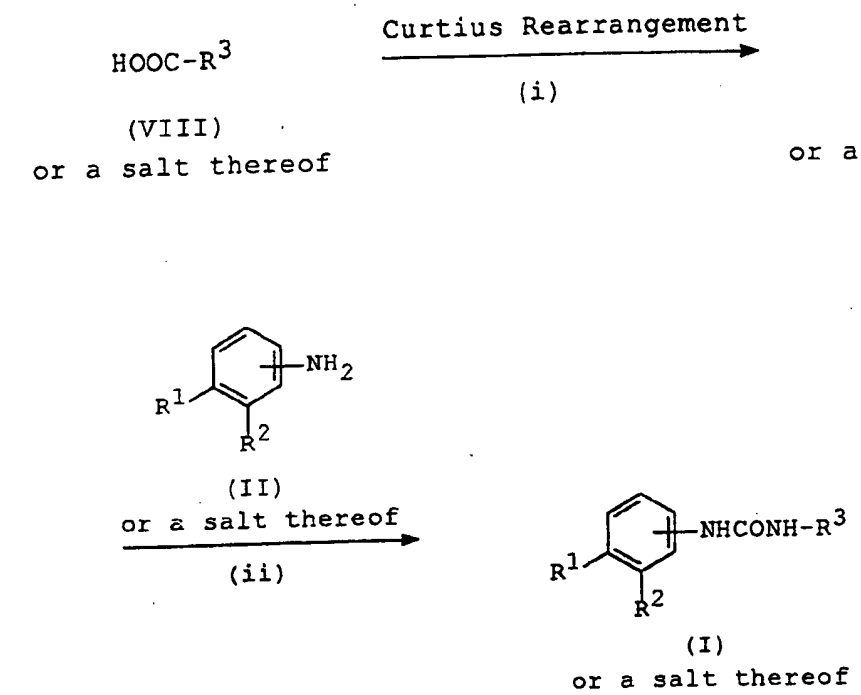
(IV)
or a salt thereof

(ii)



(I)
or a salt thereof

Process 4



wherein R^1, R^2 and R^3 are each as defined above.

Further, the object compounds (I) prepared by the above Processes 1 to 4 can be achieved conversion of their side chain within the scope of the compounds of the present invention as shown in the Examples below.

Suitable salt of the compounds (I), (II), (III), (IV), (V), (VI), (VII), (VIII) and (IX) are conventional non-toxic pharmaceutically acceptable salt and may include a salt with a base or an acid addition salt such as a salt with an inorganic base, for example, an alkali metal salt (e.g. sodium salt, potassium salt, cesium salt, etc.), an alkaline earth metal salt (e.g. calcium salt, magnesium salt, etc.),

an ammonium salt; a salt with an organic base, for example, an organic amine salt (e.g. triethylamine salt, pyridine salt, picoline salt, ethanolamine salt, triethanolamine salt, dicyclohexylamine salt, N,N'-dibenzylethylenediamine salt, etc.), etc.; an inorganic acid addition salt (e.g. hydrochloride, hydrobromide, hydroiodide, sulfate, phosphate, etc.); an organic carboxylic or sulfonic acid addition salt (e.g. formate, acetate, trifluoroacetate, maleate, tartrate, methanesulfonate, benzenesulfonate, p-toluenesulfonate, etc.); a salt with a basic or acidic amino acid (e.g. arginine, aspartic acid, glutamic acid, etc.); and the like, and the preferable example thereof is an acid addition salt.

In the above and subsequent descriptions of the present specification, suitable examples and illustrations of the various definitions which the present invention include within the scope thereof are explained in detail as follows.

The term "lower" is intended to mean 1 to 6 carbon atoms, preferably 1 to 4 carbon atoms, unless otherwise indicated.

Suitable "lower alkyl" and lower alkyl moiety in the term "lower alkylthio", "1-lower alkylindolyl", "pyridyl(lower)alkyl" and "thienyl(lower)alkyl" may include straight or branched one, having 1 to 6 carbon atom(s), such as methyl, ethyl, propyl, isopropyl, butyl, t-butyl, pentyl, hexyl, preferably one having 1 to 4 carbon atoms, and the like, in which the most preferred one is methyl, ethyl, propyl or butyl.

Suitable "lower alkylene" is one having 1 to 6 carbon atom(s) and may include methylene, ethylene, methylmethylene, trimethylene, propylene, tetramethylene, methyltrimethylene, hexamethylene, and the like, in which the preferred one is methylene or methylmethylene.

Suitable "optionally substituted aryl" includes aryl

(.g. phenyl, naphthyl, etc.) which may have suitable substituent(s) such as lower alkyl as mentioned above, lower alkoxy (e.g. methoxy, ethoxy, propoxy, etc.), halogen (e.g. fluoro, chloro, bromo, etc.), trihalo(lower)alkoxy (e.g. trifluoromethoxy, etc.), N,N-di(lower alkyl)amino (e.g. N,N-dimethylamino, etc.), and the like.

"lower alkyl which may have optionally substituted aryl" means lower alkyl as mentioned above, which may have optionally substituted aryl as mentioned above.

Suitable "4-arylpiperazin-1-yl" may include 4-phenylpiperazin-1-yl, 4-naphthylpiperazin-1-yl, and the like.

Suitable "(lower alkylimino)(optionally substituted aryl)methyl" may include (methylimino)(phenyl)methyl, and the like.

Suitable "acyl" and "acyl moiety" in the terms "acylamino" may include carbamoyl, aliphatic acyl group and acyl group containing an aromatic ring, which is referred to as aromatic acyl, or heterocyclic ring, which is referred to as heterocyclic acyl.

Suitable example of said acyl may be illustrated as follows :

Carbamoyl; Thiocarbamoyl;
Aliphatic acyl such as lower or higher alkanoyl (e.g., formyl, acetyl, propanoyl, butanoyl, 2-methylpropanoyl, pentanoyl, 2,2-dimethylpropanoyl, hexanoyl, heptanoyl, octanoyl, nonanoyl, decanoyl, undecanoyl, dodecanoyl, tridecanoyl, tetradecanoyl, pentadecanoyl, hexadecanoyl, heptadecanoyl, octadecanoyl, nonadecanoyl, icosanoyl, etc.);
lower or higher alkoxycarbonyl (e.g., methoxycarbonyl, ethoxycarbonyl, t-butoxycarbonyl, t-pentyloxycarbonyl, heptyloxycarbonyl, etc.);
lower or higher alkylsulfonyl (e.g., methylsulfonyl,

ethylsulfonyl, etc.);
lower or higher alkoxysulfonyl (e.g., methoxysulfonyl, ethoxysulfonyl, etc.);
cyclo(lower)alkylcarbonyl (e.g., cyclopentylcarbonyl, cyclohexylcarbonyl, etc.); or the like;

Aromatic acyl such as
aroyl (e.g., benzoyl, toluoyl, naphthoyl, etc.);
ar(lower)alkanoyl [e.g., phenyl(lower)alkanoyl (e.g., phenylacetyl, phenylpropanoyl, phenylbutanoyl, phenylisobutanoyl, phenylpentanoyl, phenylhexanoyl, etc.), naphthyl(lower)alkanoyl (e.g., naphthylacetyl, naphthylpropanoyl, naphthylbutanoyl, etc.), etc.];
ar(lower)alkenoyl [e.g., phenyl(lower)alkenoyl (e.g., phenylpropenoyl, phenylbutenoyl, phenylmethacryloyl, phenylpentenoyl, phenylhexenoyl, etc.), naphthyl(lower)alkenoyl (e.g., naphthylpropenoyl, naphthylbutenoyl, etc.), etc.];
ar(lower)alkoxycarbonyl [e.g., phenyl(lower)alkoxycarbonyl (e.g., benzyloxycarbonyl, etc.), etc.];
aryloxycarbonyl (e.g., phenoxycarbonyl, naphthyloxycarbonyl, etc.;
aryloxy(lower)alkanoyl (e.g., phenoxyacetyl, phenoxypropionyl, etc.);
arylglyoxyloyl (e.g., phenylglyoxyloyl, naphthylglyoxyloyl, etc.);
arylsulfonyl (e.g., phenylsulfonyl, p-tolylsulfonyl, etc.);
or the like;

Heterocyclic acyl such as
heterocycliccarbonyl;
heterocyclic(lower)alkanoyl (e.g., heterocyclicacetyl, heterocyclicpropanoyl, heterocyclicbutanoyl, heterocyclicpentanoyl, heterocyclichexanoyl, etc.);
heterocyclic(lower)alkenoyl (e.g., heterocyclicpropenoyl, heterocyclicbutenoyl, heterocyclicpentenoyl, heterocyclichexenoyl, etc.);

heterocyclicglyoxyloyl; or the like;

in which suitable "heterocyclic moiety" in the terms "heterocycliccarbonyl", "heterocyclic(lower)alkanoyl", heterocyclic(lower)alkenoyl" and "heterocyclicglyoxyloyl" as mentioned above means, in more detail, saturated or unsaturated, monocyclic or polycyclic heterocyclic group containing at least one hetero-atom such as an oxygen, sulfur, nitrogen atom and the like.

And, especially preferable heterocyclic group may be heterocyclic group such as

unsaturated 3 to 8-membered (more preferably 5 or 6-membered) heteromonocyclic group containing 1 to 4 nitrogen atom(s), for example, pyrrolyl, pyrrolinyl, imidazolyl, pyrazolyl, pyridyl, dihydropyridyl, pyrimidinyl, pyrazinyl, pyridazinyl, triazolyl (e.g., 4H-1,2,4-triazolyl, 1H-1,2,4-triazolyl, 1H-1,2,3-triazolyl, 2H-1,2,3-triazolyl, etc.), tetrazolyl (e.g., 1H-tetrazolyl, 2H-tetrazolyl, etc.), etc.;

saturated 3 to 8-membered (more preferably 5 or 6-membered) heteromonocyclic group containing 1 to 4 nitrogen atom(s), for example, pyrrolidinyl, imidazolidinyl, piperidyl, piperazinyl, etc.;

unsaturated condensed heterocyclic group containing 1 to 4 nitrogen atom(s), for example, indolyl, isoindolyl, indolinyl, indolizinyl, benzimidazolyl (e.g. 1H-benzimidazolyl, etc.), quinolyl, isoquinolyl, tetrahydroisoquinolyl (e.g. 1,2,3,4-tetrahydroisoquinolyl, etc.) indazolyl, benzotriazolyl, quinazolinyl, quinoxalinyl, phthalazinyl, etc.;

unsaturated 3 to 8-membered (more preferably 5 or 6-membered) heteromonocyclic group containing 1 to 2 oxygen atom(s) and 1 to 3 nitrogen atom(s), for example, oxazolyl, isoxazolyl, oxadiazolyl (e.g., 1,2,4-oxadiazolyl, 1,3,4-oxadiazolyl, 1,2,5-oxadiazolyl, etc.), etc.;

saturated 3 to 8-membered (more preferably 5 or 6-membered) heteromonocyclic group containing 1 to 2 oxygen

atom(s) and 1 to 3 nitrogen atom(s), for example, morpholinyl, sydnonyl, etc.;

unsaturated condensed heterocyclic group containing 1 to 2 oxygen atom(s) and 1 to 3 nitrogen atom(s), for example, benzoxazolyl, benzoxadiazolyl, etc.;

unsaturated 3 to 8-membered (more preferably 5 or 6-membered) heteromonocyclic group containing 1 to 2 sulfur atom(s) and 1 to 3 nitrogen atom(s), for example, thiazolyl, isothiazolyl, thiadiazolyl (e.g., 1,2,3-thiadiazolyl, 1,2,4-thiadiazolyl, 1,3,4-thiadiazolyl, 1,2,5-thiadiazolyl, etc.), dihydrothiazinyl, etc.;

saturated 3 to 8-membered (more preferably 5 or 6-membered) heteromonocyclic group containing 1 to 2 sulfur atom(s) and 1 to 3 nitrogen atom(s), for example, thiomorpholinyl, thiazolidinyl, etc.;

unsaturated 3 to 8-membered (more preferably 5 or 6-membered) heteromonocyclic group containing 1 to 2 sulfur atom(s), for example, thienyl, dihydrodithiinyl, dihydrodithionyl, etc.;

unsaturated condensed heterocyclic group containing 1 to 2 sulfur atom(s) and 1 to 3 nitrogen atom(s), for example, benzothiazolyl, benzothiadiazolyl, etc.;

unsaturated 3 to 8-membered (more preferably 5 or 6-membered) heteromonocyclic group containing an oxygen atom, for example, furyl, etc.;

unsaturated 3 to 8-membered (more preferably 5 or 6-membered) heteromonocyclic group containing an oxygen atom and 1 to 2 sulfur atom(s), for example, dihydrooxathiinyl, etc.;

unsaturated condensed heterocyclic group containing 1 to 2 sulfur atom(s), for example, benzothienyl, benzodithiinyl, etc.;

unsaturated condensed heterocyclic group containing an oxygen atom and 1 to 2 sulfur atom(s), for example, benzoxathiinyl, etc.; and the like.

The acyl moiety as stated above may have one to ten, same or different, suitable substituent(s).

The preferred embodiments of R^1, R^2 and R^3 are as follows.

R^1 is cyano, thiocarbamoyl,

a group of the formula :

$$-(A^1-NH)_m-\overset{\overset{NH}{\|}}{C}-(NH)_n-R^4$$

wherein R^4 is hydrogen, lower alkyl, phenyl(lower)alkyl, di(lower alkoxy)phenyl(lower)alkyl, phenyl(lower)alkoxycarbonyl, phenyl, lower alkoxyphenyl, lower alkylthio or 1-lower alkylindolyl,

A^1 is lower alkylene, and

m and n are each 0 or 1,

a group of the formula :

$$-A^2-R^5$$

wherein R^5 is morpholino, piperidino, 4-phenylpiperazin-1-yl, phthalimido, 1,2,3,4-tetrahydroquinolin-1-yl, 1,2,3,4-tetrahydroisoquinolin-2-yl or imidazol-1-yl, and

A^2 is lower alkylene, or

a group of the formula :

$$-A^3-\overset{\overset{R^6}{|}}{N}-R^7$$

wherein R^6 and R^7 are each hydrogen, phenyl, lower alkanoyl, phenyl(lower)alkoxycarbonyl,

pyridyl(lower)alkyl, thienyl(lower)alkyl, 3,4-dihydroisoquinolinyl, (lower alkylimino)(phenyl)methyl, lower alkyl, phenyl(lower)alkyl, naphthyl(lower)alkyl, (mono- or di- or trilower alkyl)phenyl-(lower)alkyl, (mono- or di- or trilower alkoxy)phenyl(lower)alkyl, (mono- or di- or trihalo)phenyl(lower)alkyl, [trihalo(lower)alkoxy]phenyl(lower)alkyl or [lower alkoxy][trihalo(lower)alkoxy]-phenyl(lower)alkyl, and

A^3 is lower alkylene, and

R^2 is hydrogen; or

R^1 and R^2 are linked together to form

$$-(CH_2)_3-\underset{\displaystyle R^8}{\underset{|}{CH}}-\ ,$$

$$-(CH_2)_2-\underset{\displaystyle R^9}{\underset{|}{N}}-CH_2-\ ,\ \text{or}$$

$$-(CH_2)_3-\underset{\displaystyle R^9}{\underset{|}{N}}-\ ,$$

wherein R^8 is amino or lower alkanoylamino, and

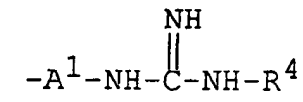
R^9 is hydrogen, phenyl(lower)alkoxycarbonyl or phenyl(lower)alkyl, and

R^3 is 1-lower alkylindolyl, benzofuranyl, dihydrobenzofuranyl, or N,N-di(lower alkyl)aminophenyl.

Further, the preferred embodiments of R^1, R^2 and R^3 are as follows.

R^1 is cyano, thiocarbamoyl,

a group of the formula :

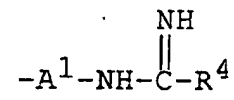


wherein R^4 is hydrogen or phenyl(lower)alkoxycarbonyl,

and

A^1 is lower alkylene,

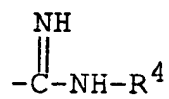
a group of the formula :



wherein R^4 is phenyl or 1-lower alkylindolyl, and

A^1 is lower alkylene,

a group of the formula :

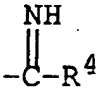


wherein R^4 is hydrogen, lower alkyl, phenyl(lower)alkyl,

di(lower alkoxy)phenyl(lower)alkyl,

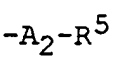
phenyl or lower alkoxyphenyl,

a group of the formula :



wherein R^4 is lower alkylthio,

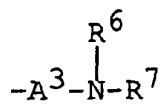
a group of the formula :



wherein R^5 is morpholino, piperidino, 4-phenylpiperazin-1-yl, phthalimido, 1,2,3,4-tetrahydroquinolin-1-yl, 1,2,3,4-tetrahydroisoquinolin-2-yl or imidazol-1-yl, and

A^2 is lower alkylene, or

a group of the formula :



wherein R^6 and R^7 are each hydrogen, phenyl, lower alkanoyl, phenyl(lower)alkoxycarbonyl, pyridyl(lower)alkyl, thienyl(lower)alkyl, 3,4-dihydroisoquinolinyl, (lower alkylimino)(phenyl)methyl, lower alkyl, phenyl(lower)alkyl, naphthyl(lower)alkyl, (mono- or di- or trilower alkyl)phenyl(lower)alkyl, (mono- or di- or trilower alkoxy)phenyl(lower)alkyl, (mono- or di- or trihalo)phenyl(lower)-alkyl, [trihalo(lower)alkoxy]phenyl-(lower)alkyl or [lower alkoxy][trihalo-(lower)alkoxy]phenyl(lower)alkyl, and

A^3 is lower alkylene,

R^2 is hydrogen and

R^3 is 1-lower alkylindolyl, benzofuranyl, dihydrobenzofuranyl or N,N-di(lower alkyl)aminophenyl.

The processes 1 to 4 for preparing the object compounds (I) of the present invention are explained in detail in the following.

Process 1 :

The object compound (I) or a salt thereof can be

pr par d by reacting the compound (II) or a salt thereof with 1,1'-carbonyldiimidazole and continuously by reacting the obtained compound (III) or a salt thereof with the compound (IV) or a salt thereof.

The present reaction is usually carried out in a solvent such as dioxane, dimethylsulfoxide, dimethylformamide, diethylformamide, dimethylacetamide, benzene, hexane, tetrahydrofuran, or any other solvent which does not adversely affect the reaction.

The reaction temperature is not critical and the reaction is usually carried out under cooling, at ambient temperature or under heating.

Process 2 :

The object compound (I) or a salt thereof can be prepared by reacting the compound (IV) or a salt thereof with 1,1'-carbonyldiimidazole and continuously by reacting the obtained compound (V) or a salt thereof with the compound (II) or a salt thereof.

The reaction can be carried out in a similar manner to that of the aforementioned Process 1.

Process 3 :

The object compound (I) or a salt thereof can be prepared by subjecting the compound (VI) or a salt thereof to Curtius Rearrangement reaction and continuously by reacting the obtained compound (VII) or a salt thereof with the compound (IV) or a salt thereof.

Curtius Rearrangement reaction may carried out by using a conventional reagent such as diphenylphosphoryl azide.

The reaction may be also carried out in the presence of an organic or inorganic base such as an alkali metal bicarbonate, tri(lower)alkylamine, pyridine, N-(lower)alkylmorphorine, N,N-di(lower)alkylbenzylamine, or the like.

The reaction temperature is not critical, and the reaction is usually carried out under cooling to heating.

Process 4 :

The object compound (I) or a salt thereof can be prepared by subjecting the compound (VIII) or a salt thereof to Curtius Rearrangement reaction and continuously by reacting the obtained compound (IX) or a salt thereof with the compound (II) or a salt thereof.

This reaction can be carried out in a similar manner to that of the aforementioned Process 3.

The object compound (I) of the present invention can be isolated and purified in a conventional manner, for example, extraction, precipitation, fractional crystallization, recrystallization, chromatography, and the like.

The object compound (I) thus obtained can be converted to its salt by a conventional method.

The object compound (I) and a pharmaceutically acceptable salt thereof may include a solvate [e.g., enclosure compound (e.g., hydrate, etc.)].

The object compound (I) of the present invention are novel and exhibit pharmacological activities such as 5-HT antagonism, especially, 5-HT_{2C} antagonism, and the like and therefore are useful as 5-HT antagonist for treating or preventing central nervous system (CNS) disorders such as anxiety, depression, obsessive compulsive disorders, migraine, anorexia, Alzheimer's disease, sleep disorders, bulimia, panic attacks, withdrawal from drug abuse such as cocaine, ethanol, nicotine and benzodiazepines, schizophrenia, and also disorders associated with spinal trauma and/or head injury such as hydrocephalus, and the like.

In order to illustrate the usefulness of the object

compounds (I), pharmacological activity of representative compound of the present invention are shown below.

Test Method :

$[^3H]$-mesulergine binding

The affinity of test drugs for the 5-HT_{2C} binding site can be determined by assessing their ability to displace $[^3H]$-mesulergine in the rat prefrontal cortex. The method employed was similar to that of Pazos et al, 1984.

The membrane suspension (500 µl) was incubated with $[^3H]$-mesulergine (1 nM) in Tris HCl buffer containing $CaCl_2$ 4 mM and ascorbic acid 0.1% (pH 7.4) at 37°C for 30 minutes. Non-specific binding was measured in the presence of mianserin (1 µM). 30 nM spiperone was used to prevent binding to 5-HT_{2A} sites. Test drugs (10^{-6} M) were added in a volume of 100 µl. The total assay volume was 1000 µl. Incubation was stopped by rapid filtration using a Brandel cell harvester and radioactivity measured by scintillation counting.

The IC_{50} values were determined using a four parameter logistic program (DeLean 1978) and the pKi (the negative logarithm of the inhibition constant) calculated from the Cheng Prusoff equation where :

$$Ki = \frac{IC_{50}}{1+C/Kd}$$

Ki = inhibition constant
C = concentration of $[^3H]$-mesulergine
Kd = affinity of mesulergine for 5-HT_{2C} binding sites.

Test Compounds :

(1) N-(1-Methyl-1H-indol-5-yl)-N'-(3-pyridyl)urea (Reference compound (A))

(2) N-[3-(Butylamidino)phenyl]-N'-[1-methyl-1H-indol-5-yl]urea hydroiodide

(3) N-[3-(Benzylamidino)phenyl]-N'-[1-methyl-1H-indol-5-yl]urea hydroiodide

(4) N-[3-[2-(3,4-Dimethoxyphenyl)ethyl]amidinophenyl]-N'-[1-methyl-1H-indol-5-yl]urea hydroiodide

Test Result :

Compound	Inhibition (%)
(1)	21
(2)	77
(3)	83
(4)	82

For therapeutic or preventive administration, the object compound (I) of the present invention are used in the form of conventional pharmaceutical preparation which contains said compound as an active ingredient, in admixture with pharmaceutically acceptable carriers such as an organic or inorganic solid or liquid excipient which is suitable for oral, parenteral and external administration. The pharmaceutical preparations may be in solid form such as tablet, granule, powder, capsule, or liquid form such as solution, suspension, syrup, emulsion, lemonade and the like.

If needed, there may be included in the above preparations auxiliary substances, stabilizing agents,

wetting agents and other commonly used additives such as lactose, citric acid, tartaric acid, stearic acid, magnesium stearate, terra alba, sucrose, corn starch, talc, gelatin, agar, pectin, peanut oil, olive oil, cacao butter, ethylene glycol, and the like.

While the dosage of the compound (I) may vary from and also depend upon the age, conditions of the patient, a kind of diseases or conditions, a kind of the compound (I) to be applied, etc. In general amounts between 0.01 mg and about 500 mg or even more per day may be administered to a patient. An average single dose of about 0.05 mg, 0.1 mg, 0.25 mg, 0.5 mg, 1 mg, 20 mg, 50 mg, 100 mg of the object compound (I) of the present invention may be used in treating diseases.

The following Preparations and Examples are given for the purpose of illustrating the present invention.

Preparation 1

A mixture of 3-nitrobenzyl bromide (1 g) and 4-methoxybenzylamine (2.26 g) in chloroform (20 ml) was refluxed for 3 hours. This solution was washed with 1N aqueous sodium hydroxide solution twice, dried over magnesium sulfate, filtered, and evaporated. The residue was chromatographed on silica gel (hexene:chloroform = 1:1) to give N-(4-methoxybenzyl)-3-nitrobenzylamine.

IR (Film) : 3300, 1600, 1580 cm^{-1}

NMR (DMSO-d_6, δ) : 2.80 (1H, s), 3.62 (2H, s), 3.79 (3H, s), 3.87 (2H, s), 6.85-6.88 (2H, m), 7.23-7.27 (2H, m), 7.60 (1H, t, J=7.9Hz), 7.78 (1H, d, J=7.6Hz), 8.09 (1H, d, J=8.1Hz), 8.38 (1H, s)

Preparation 2

A mixture of 3-nitrobenzyl chloride (1.01 g), diphenylamine (500 mg), potassium hydroxide (993 mg), potassium carbonate (652 mg) and tetra-n-butylammonium

sulfate (79 mg) in toluene (30 ml) was stirred at 72°C for 3 hours. The mixture was washed with water, dried over magnesium sulfate, filtered, and evaporated. This oil was chromatographed on silica gel (hexane:ethyl acetate = 8:1) to give N-(3-nitrobenzyl)diphenylamine.

IR (Nujol) : 1580, 1520 cm^{-1}

NMR (DMSO-d_6, δ) : 5.16 (2H, s), 6.90-7.31 (12H, m), 7.62 (1H, t, J=7.8Hz), 7.80 (1H, d, J=7.7Hz), 8.08 (1H, d, J=8.1Hz), 8.19 (1H, s)

MASS : 305 (M+1)

Preparation 3

A mixture of N-(4-methoxybenzyl)-3-nitrobenzylamine (1.8 g), benzyloxycarbonyl chloride (1 ml) and triethylamine (1 ml) in toluene (15 ml) was stirred at ambient temperature for 3 hours. This solution was washed with water twice, dried over magnesium sulfate, filtered, and evaporated. The residue was chromatographed on silica gel (chloroform) to give N-(benzyloxycarbonyl)-N-(4-methoxybenzyl)-3-nitrobenzylamine.

IR (Film) : 3450, 1690, 1600 cm^{-1}

NMR (DMSO-d_6, δ) : 3.72 (3H, s), 4.45 (2H, s), 4.54 (2H, s), 5.16 (2H, s), 6.84-6.88 (2H, m), 7.11-8.11 (11H, m)

Preparation 4

The following compound was obtained according to a similar manner to that of Preparation 3.

N-(Benzyloxycarbonyl)-N-(4-methylbenzyl)-3-nitrobenzylamine

IR (Film) : 3000, 2900, 1680 cm^{-1}

NMR (DMSO-d_6, δ) : 2.27 (3H, s), 4.47 (2H, s), 4.54 (2H, s), 5.16 (2H, s), 7.12-7.4 (9H, m), 7.5-7.8 (2H, m), 7.90-8.12 (2H, m)

Preparation 5

A mixture of N-(3-nitrobenzyl)diphenylamine (400 mg), ferric chloride (150 mg), active carbon (700 mg) and hydrazine monohydrate (260 mg) in ethanol (15 ml) was stirred at 70°C for 2 hours. The mixture was filtered, evaporated. The residue was dissolved in chloroform, washed with water, dried over sodium sulfate, filtered, and evaporated to give 3-(N,N-diphenylaminomethyl)aniline.

IR (Nujol) : 1575, 1520 cm^{-1}

NMR (DMSO-d_6, δ) : 4.83 (2H, s), 5.01 (2H, s), 6.36-6.47 (2H, m), 6.56 (1H, s), 6.86-7.28 (11H, m)

MASS : 275 (M+1)

Example 1

A solution of m-aminobenzonitrile (3.01 g) and 1,1'-carbonyldiimidazole (4.14 g) in tetrahydrofuran (30 ml) was stirred at room temperature for 5 hours. A solution of 5-amino-1-methylindole (2.48 g) in tetrahydrofuran (20 ml) was added to the solution. The solution was stirred at room temperature for 48 hours. After evaporation of the solvent, the residue was dissolved in chloroform-methanol (7:3, V/V). The solution was evaporated in vacuo to the volume of 15 ml. The solution was diluted with methanol and allowed to stand at room temperature overnight. The crystals formed was collected and washed with methanol to give N-(3-cyanophenyl)-N'-(1-methyl-1H-indol-5-yl)urea (2.48 g). From the filtrate, another crop of the product (0.82 g) was obtained in a similar manner to that described above.

mp : 203-208°C

IR (Nujol) : 3280, 2220, 1630, 1555 cm^{-1}

NMR (DMSO-d_6, δ) : 3.76 (3H, s), 6.35 (1H, d, J=3Hz), 7.14-7.75 (7H, m), 8.00 (1H, s), 8.60 (1H, s), 8.93 (1H, s)

Example 2

To a solution of N-(3-cyanophenyl)-N'-(1-methyl-1H-indol-5-yl)urea (2.99 g) in pyridine (30 ml) and triethylamine (10 ml) was passed through slowly hydrogen sulfide gas for 8 hours at room temperature. After 12 hours the solution was diluted with water and stirred for 2 hours. The precipitate formed was collected and washed with water to give N-(1-methyl-1H-indol-5-yl)-N'-(3-thiocarbamoylphenyl)-urea (3.19 g).

mp : 211-214°C

IR (Nujol) : 3290, 3180, 1625, 1604, 1568 cm^{-1}

NMR (DMSO-d_6, δ) : 3.76 (3H, s), 6.34 (1H, d, J=3Hz), 7.12-7.70 (7H, m), 7.95 (1H, s), 8.42 (1H, s), 8.76 (1H, s), 9.46 (1H, s), 9.84 (1H, s)

Example 3

To a solution of N-(1-methyl-1H-indol-5-yl)-N'-(3-thiocarbamoylphenyl)urea (1.87 g) in a mixture of acetonitrile (8 ml) and N,N-dimethylformamide (15 ml) was added methyliodide (2 ml). After 24 hours, the solution was diluted with ether. The precipitate formed was collected and washed with ether to give N-(1-methyl-1H-indol-5-yl)-N'-[3-[methylthio(imino)methyl]phenyl]urea hydroiodide (2.60 g).

mp : 187-196°C

IR (Nujol) : 3270, 3150, 1675, 1590, 1555 cm^{-1}

NMR (DMSO-d_6, δ) : 2.85 (3H, s), 3.77 (3H, s), 6.36 (1H, d, J=3Hz), 7.15-7.70 (8H, m), 8.22 (1H, s), 8.60 (1H, s), 9.03 (1H, s)

Example 4

A mixture of N-(1-methyl-1H-indol-5-yl)-N'-[3-[methylthio(imino)methyl]phenyl]urea (0.51 g) and aniline (0.20 g) in N,N-dimethylformamide (3 ml) was stirred at 70°C for 8 hours. After evaporation of the solvent, the residue was neutralized with 1N aqueous sodium hydroxide solution and extracted twice with butanol. The butanol layer was

evaporated in vacuo. The residue was purified by column chromatography on silica gel (15% methanol in chloroform) to give N-[1-methyl-1H-indol-5-yl]-N'-[3-(phenylamidino)-phenyl]urea (80 mg) as an amorphous powder.

IR (Nujol) : 3430, 3300, 1690, 1630, 1570 cm^{-1}

NMR (DMSO-d_6, δ) : 3.75 (3H, s), 6.22 (1H, br s), 6.34 (1H, d, J=3Hz), 6.80-7.60 (13H, m), 7.70 (1H, d, J=2Hz), 8.03 (1H, s), 8.42 (1H, s), 8.70 (1H, s)

Example 5

A mixture of N-(1-methyl-1H-indol-5-yl)-N'-[3-[methylthio(imino)methyl]phenyl]urea (0.60 g) and ammonium acetate (0.30 g) in methanol (6 ml) was heated at 65°C for 7 hours. After cooling, the precipitate formed was collected and washed with methanol to give N-(3-amidinophenyl)-N'-(1-methyl-1H-indol-5-yl)urea hydroiodide (75 mg).

mp : 214-218°C

IR (Nujol) : 3340, 3260, 1690, 1640, 1560, 1525 cm^{-1}

NMR (DMSO-d_6, δ) : 3.75 (3H, s), 6.32 (1H, d, J=3Hz), 7.20-7.80 (9H, m), 7.97 (1H, s), 9.60-10.40 (4H, m)

Example 6

A mixture of N-(1-methyl-1H-indol-5-yl)-N'-[3-[methylthio(imino)methyl]phenyl]urea (300 mg), butylamine (188 mg), and acetic acid (154 mg) in methanol (3 ml) was stirred at 60°C for 6 hours. After evaporation of the solvent, the residue was washed once with ether and twice with water. The oil was dissolved in methanol and the solution was evaporated in vacuo. The residue was triturated with ether and the powder obtained was collected and washed with ether to give N-[3-(butylamidino)phenyl]-N'-[1-methyl-1H-indol-5-yl]urea hydroiodide (274 mg) as an amorphous powder.

IR (Nujol) : 3250, 1660, 1590, 1540 cm^{-1}

NMR (DMSO-d_6, δ) : 0.93 (3H, t, J=7Hz), 1.39 (2H, m),

1.61 (2H, m), 3.36 (2H, t, J=7Hz), 3.75 (3H, s), 6.33 (1H, d, J=3Hz), 7.10-6.80 (7H, m), 8.00 (1H, s), 9.66 (1H, s), 10.10 (1H, s)

Example 7

N-[3-(Benzylamidino)phenyl]-N'-[1-methyl-1H-indol-5-yl]urea hydroiodide was prepared in a similar manner to that of Example 6.

IR (Nujol) : 3250, 1660, 1620, 1580, 1540 cm^{-1}

NMR (DMSO-d_6, δ) : 3.76 (3H, s), 4.66 (2H, s), 6.35 (1H, d, J=3Hz), 7.10-7.70 (12H, m), 7.99 (1H, s), 8.59 (1H, s), 8.96 (1H, s), 8.60-9.60 (3H, br s)

Example 8

N-[3-[2-(3,4-Dimethoxyphenyl)ethyl]amidinophenyl]-N'-[1-methyl-1H-indol-5-yl]urea hydroiodide was prepared in a similar manner to that of Example 6.

IR (Nujol) : 3250, 1665, 1585, 1560 cm^{-1}

NMR (DMSO-d_6, δ) : 2.90 (2H, br t, J=7Hz), 3.62 (2H, br t, J=7Hz), 3.72 (3H, s), 3.76 (6H, s), 6.34 (1H, d, J=3Hz), 6.70-7.80 (9H, m), 8.00 (1H, s), 9.03 (1H, s), 9.41 (1H, s)

Example 9

N-[3-(4-Methoxyphenylamidino)phenyl]-N'-[1-methyl-1H-indol-5-yl]urea hydroiodide was prepared in a similar manner to that of Example 6.

IR (Nujol) : 3250, 1660, 1600, 1550, 1510 cm^{-1}

NMR (DMSO-d_6, δ) : 3.76 (3H, s), 3.82 (3H, s), 6.35 (1H, d, J=3Hz), 7.10-7.75 (12H, m), 8.12 (1H, s), 8.61 (1H, s), 8.97 (1H, s)

Example 10

N-(Benzofuran-5-yl)-N'-(3-cyanophenyl)urea was prepared in a similar manner to that of Example 1.

mp : 180-187°C

IR (Nujol) : 3270, 2230, 1630, 1600, 1560 cm^{-1}

NMR (DMSO-d_6, δ) : 6.93 (1H, m), 7.25-8.00 (8H, m), 8.83 (1H, s), 9.00 (1H, s)

Example 11

N-(Benzofuran-5-yl)-N'-(3-thiocarbamoylphenyl)urea was prepared in a similar manner to that of Example 2.

mp : 188-194°C

IR (Nujol) : 3280, 3170, 1625, 1600, 1565 cm^{-1}

NMR (DMSO-d_6, δ) : 6.92 (1H, m), 7.25-8.00 (8H, m), 8.66 (1H, s), 8.84 (1H, s), 9.46 (1H, s), 9.84 (1H, s)

Example 12

N-(Benzofuran-5-yl)-N'-[3-[methylthio(imino)methyl]-phenyl]urea hydroiodide was prepared in a similar manner to that of Example 3.

mp : 190-196°C

IR (Nujol) : 3180, 1675, 1590, 1550 cm^{-1}

NMR (DMSO-d_6, δ) : 2.86 (3H, s), 6.94 (1H, m), 7.30-8.20 (8H, m), 8.84 (1H, s), 9.12 (1H, s)

Example 13

10% Pd-C (100 mg) was added to a solution of 1-methyl-5-nitroindole (500 mg) in ethanol (20 ml). This mixture was hydrogenated at 1 atm at ambient temperature for 2 hours. The mixture was filtered through celite and evaporated. The resulting oil was coevaporated with toluene. To the resulting mass, 1,1'-carbonyldiimidazole (460 mg) was added. This mixture was stirred at ambient temperature for 4 hours. To this solution, 3-(dimethylaminomethyl)aniline (341 mg) was added. This mixture was stirred at ambient temperature overnight, evaporated, and partitioned between chloroform (50 ml) and water (20 ml). The organic layer was washed with

water (2 x 20 ml), dried with magnesium sulfate, filtered, and evaporated. The residue was chromtographed over silica gel (chloroform) and recrystallized from methanol - ethyl acetate to give N-(3-dimethylaminomethylphenyl)-N'-(1-methylindol-5-yl)urea.

mp : 128-133°C

IR (Nujol) : 1630 cm^{-1}

NMR (DMSO-d_6, δ) : 2.16 (6H, s), 2.96 (1H, d, J=3.0Hz), 3.75 (3H, s), 6.86 (1H, d, J=6.9Hz), 7.12-7.35 (5H, m), 7.45 (1H, s), 7.69 (1H, d, J=1.7Hz), 8.42 (1H, s), 8.59 (1H, s)

Example 14

N-(1-Methylindol-5-yl)-N'-[3-[(4-phenylpiperazin-1-yl)methyl]phenyl]urea was prepared in a similar manner to that of Example 13.

mp : 183-185°C

IR (Nujol) : 1610 cm^{-1}

NMR (DMSO-d_6, δ) : 2.4-2.6 (4H, m), 3.08-3.23 (4H, m), 3.49 (2H, s), 3.75 (3H, s), 6.34 (1H, d, J=3.0Hz), 6.76 (1H, t, J=7.3Hz), 6.89-6.94 (3H, m), 7.11-7.38 (7H, m), 7.47 (1H, s), 7.68 (1H, s), 8.39 (1H, s), 8.59 (1H, s)

Example 15

N-(1-Methylindol-5-yl)-N'-(3-piperidinomethylphenyl)urea was prepared in a similar manner to that of Example 13.

mp : 172-173°C

IR (Nujol) : 1625 cm^{-1}

NMR (DMSO-d_6, δ) : 1.3-1.6 (6H, m), 2.25-2.45 (4H, m), 3.37 (2H, s), 3.75 (3H, s), 6.34 (1H, d, J=3.0Hz), 6.85 (1H, d, J=7.4Hz), 7.11-7.40 (6H, m), 7.68 (1H, d, J=1.8Hz), 8.36 (1H, s), 8.56 (1H, s)

Example 16

N-(1-Methylindol-5-yl)-N'-(3-morpholinomethylphenyl)urea was prepared in a similar manner to that of Example 13.

mp : 174-175°C

IR (Nujol) : 1650, 1615 cm^{-1}

NMR (DMSO-d_6, δ) : 2.36 (4H, t, J=4.4Hz), 3.42 (2H, s), 3.58 (4H, t, J=4.4Hz), 3.75 (3H, s), 6.34 (1H, d, J=2.7Hz), 6.88 (1H, d, J=7.4Hz), 7.11-7.36 (5H, m), 7.44 (1H, s), 7.69 (1H, d, J=1.8Hz), 8.38 (1H, s), 8.57 (1H, s)

Example 17

N-(1-Methylindol-5-yl)-N'-(4-phthalimidomethylphenyl)-urea was prepared in a similar manner to that of Example 13.

IR (Nujol) : 1760, 1700, 1665 cm^{-1}

NMR (DMSO-d_6, δ) : 3.75 (3H, s), 4.41 (2H, s), 6.33 (1H, d, J=3Hz), 7.12 (1H, dd, J=9Hz, 2Hz), 7.20-7.45 (6H, m), 7.67 (1H, d, J=2Hz), 7.80-7.95 (4H, m), 8.40 (1H, s), 8.59 (1H, s)

Example 18

N-[3-(1-Formylaminoethyl)phenyl]-N'-[1-methylindol-5-yl]urea was prepared in a similar manner to that of Example 13.

mp : 165-168°C

IR (Nujol) : 1650, 1635 cm^{-1}

NMR (DMSO-d_6, δ) : 1.36 (3H, d, J=7Hz), 3.75 (3H, s), 4.80-5.10 (1H, m), 6.34 (1H, d, J=3Hz), 6.80-6.95 (1H, m), 7.10-7.50 (6H, m), 7.69 (1H, d, J=2Hz), 8.03 (1H, s), 8.40 (1H, s), 8.50-8.60 (2H, m)

MASS : 337 ($M+1^{\oplus}$)

Example 19

N-[3-(N-Methylanilino)methylphenyl]-N'-(1-methylindol-5-yl)urea was prepared in a similar manner to that of Example 13.

mp : 143-144°C

IR (Nujol) : 1610 cm^{-1}

NMR (DMSO-d_6, δ) : 3.02 (3H, s), 3.75 (3H, s), 4.52 (2H, s), 7.33 (1H, d, J=3.0Hz), 6.60-6.81 (4H, m), 7.09-7.40 (8H, m), 7.67 (1H, d, J=1.7Hz), 8.35 (1H, s), 8.54 (1H, s)

MASS : 385 (M+1)

Example 20

N-(1-Methylindol-5-yl)-N'-[3-(1,2,3,4-tetrahydroquinolin-1-yl)methylphenyl]urea was prepared in a similar manner to that of Example 13.

mp : 181-184°C

IR (Nujol) : 1610 cm^{-1}

NMR (DMSO-d_6, δ) : 1.19-1.99 (2H, m), 2.74 (2H, t, J=6.1Hz), 3.38 (2H, t, J=5.4Hz), 3.75 (3H, s), 4.43 (2H, s), 6.33-6.34 (1H, m), 6.42-6.49 (2H, m), 6.82-6.91 (3H, m), 7.10-7.40 (6H, m), 7.66 (1H, s), 8.33 (1H, s), 8.53 (1H, s)

MASS : 411 (M+1)

Example 21

N-(1-Methylindol-5-yl)-N'-(3-anilinomethylphenyl]urea was prepared in a similar manner to that of Example 13.

mp : 129-131°C

IR (Nujol) : 1610 cm^{-1}

NMR (DMSO-d_6, δ) : 3.75 (3H, s), 4.22 (2H, d, J=5.9Hz), 6.19 (1H, t, J=5.8Hz), 6.33 (1H, d, J=2.9Hz), 6.47-6.59 (2H, m), 6.92-7.40 (9H, m), 7.67 (1H, s), 8.35 (1H, s), 8.52 (1H, s)

MASS : 371 (M+1)

Example 22

N-(1-Methylindol-5-yl)-N'-[3-(1,2,3,4-tetrahydroisoquinolin-2-yl)methylphenyl]urea was prepared in a similar manner to that of Example 13.

mp : 189-190°C

IR (Nujol) : 1620, 1540 cm^{-1}

NMR (DMSO-d_6, δ) : 2.70 (2H, d, J=5.2Hz), 2.81 (2H, d, J=5.2Hz), 3.54 (2H, s), 3.61 (2H, s), 3.75 (3H, s), 6.33 (1H, d, J=3.0Hz), 6.91-7.50 (10H, m), 7.68 (1H, s), 7.69 (1H, s), 8.37 (1H, s), 8.56 (1H, s)

MASS : 411 (M+1)

Example 23

N-(1-Methylindol-5-yl)-N'-(3-phthalimidomethylphenyl)-urea was prepared in a similar manner to that of Example 13.

mp : 222-226°C

IR (Nujol) : 1700, 1610 cm^{-1}

NMR (DMSO-d_6, δ) : 3.75 (3H, s), 4.74 (2H, s), 6.33 (1H, d, J=3.0Hz), 6.87-7.44 (8H, m), 7.84-7.95 (4H, m), 8.56 (1H, s), 8.80 (1H, s)

MASS : 425 (M+1)

Example 24

N-(1-Methylindol-5-yl)-N'-(3-diphenylaminomethylphenyl)-urea was prepared in a similar manner to that of Example 13.

mp : 194-195°C

IR (Nujol) : 1610 cm^{-1}

NMR (DMSO-d_6, δ) : 3.75 (3H, s), 4.97 (2H, s), 6.33 (1H, d, J=3.0Hz), 6.88-7.40 (17H, m), 7.66 (1H, d, J=1.8Hz), 8.35 (1H, s), 8.57 (1H, s)

MASS : 447 (M+1)

Example 25

N-[3-(1-Anilinoethyl)phenyl]-N'-(1-methylindol-5-yl)urea was prepared in a similar manner to that of Example 13.

mp : 158-162°C

IR (Nujol) : 1650, 1600 cm^{-1}

NMR (DMSO-d_6, δ) : 1.42 (3H, d, J=7Hz), 3.75 (3H, s), 4.38 (1H, quint., J=7Hz), 6.14 (1H, d, J=6Hz), 6.33

(1H, d, J=3Hz), 6.40-6.55 (3H, m), 6.90-7.45 (9H, m), 7.68 (1H, s), 8.36 (1H, s), 8.52 (1H, s)
MASS : 385 ($M+1^{\oplus}$)

Example 26

N-[3-(Imidazol-1-ylmethyl)phenyl]-N'-(1-methylindol-5-yl)urea was prepared in a similar manner to that of Example 13.

mp : 170-175°C
IR (Nujol) : 1630 cm^{-1}
NMR (DMSO-d_6, δ) : 3.75 (3H, s), 5.17 (2H, s), 6.34 (1H, d, J=3Hz), 6.82 (1H, d, J=8Hz), 6.92 (1H, s), 7.05-7.45 (7H, m), 7.68 (1H, d, J=2Hz), 7.75 (1H, s), 8.40 (1H, s), 8.61 (1H, s)
MASS : 346 ($M+1^{\oplus}$)

Example 27

N-(8-Formylamino-5,6,7,8-tetrahydro-2-naphthyl)-N'-(1-methylindol-5-yl)urea was prepared in a similar manner to that of Example 13.

IR (Nujol) : 1630 cm^{-1}
NMR (DMSO-d_6, δ) : 1.60-2.00 (4H, m), 2.66 (2H, br s), 3.75 (3H, s), 5.00-5.10 (1H, m), 6.33 (1H, d, J=3Hz), 6.99 (1H, d, J=8Hz), 7.11 (1H, dd, J=9Hz, 2Hz), 7.20-7.40 (4H, m), 7.67 (1H, d, J=2Hz), 8.12 (1H, s), 8.30 (1H, s), 8.40-8.60 (2H, m)

Example 28

N-(2-Benzyloxycarbonyl-1,2,3,4-tetrahydroisoquinolin-7-yl)-N'-(1-methylindol-5-yl)urea was prepared in a similar manner to that of Example 13.

mp : 218-222°C
IR (Nujol) : 1700, 1660, 1615 cm^{-1}
NMR (DMSO-d_6, δ) : 2.73 (2H, br t, J=6Hz), 3.62 (2H, br t, J=6Hz), 3.75 (3H, s), 4.55 (2H, br s), 5.13 (2H, s), 6.33 (1H, d, J=3Hz), 7.03-7.40 (6H, m), 7.68 (1H, d, J=2Hz), 8.43 (1H, br s), 8.49 (1H, br s)

MASS : 455 ($M+1^{\oplus}$)

Example 29

N-(2-Benzyloxycarbonyl-1,2,3,4-tetrahydroisoquinolin-5-yl)-N'-(1-methylindol-5-yl)urea was prepared in a similar manner to that of Example 13.

mp : 153-156°C

IR (Nujol) : 1690, 1630 cm^{-1}

NMR (DMSO-d_6, δ) : 2.71 (2H, br t, J=6Hz), 3.69 (2H, br t, J=6Hz), 3.75 (3H, s), 4.59 (2H, br s), 5.13 (2H, s), 6.33 (1H, d, J=3Hz), 6.88 (1H, d, J=8Hz), 7.10-7.40 (9H, m), 7.60-7.80 (2H, m), 7.88 (1H, br s), 8.76 (1H, br s)

MASS : 455 ($M+1^{\oplus}$)

Example 30

N-(2-Benzyl-1,2,3,4-tetrahydroisoquinolin-7-yl)-N'-(1-methylindol-5-yl)urea was prepared in a similar manner to that of Example 13.

mp : 165-167°C

IR (Nujol) : 1635 cm^{-1}

NMR (DMSO-d_6, δ) : 2.55-2.80 (4H, m), 3.50 (2H, s), 3.64 (2H, s), 3.75 (3H, s), 6.32 (1H, d, J=3Hz), 6.90-7.40 (11H, m), 7.66 (1H, s), 8.37 (2H, br s)

MASS : 411 ($M+1^{\oplus}$)

Example 31

N-(1-Benzyloxycarbonyl-1,2,3,4-tetrahydroquinolin-7-yl)-N'-(1-methylindol-5-yl)urea was prepared in a similar manner to that of Example 13.

IR (Nujol) : 1680, 1640, 1610 cm^{-1}

NMR (DMSO-d_6, δ) : 1.84 (2H, quar., J=6Hz), 2.67 (2H, t, J=6Hz), 3.60-3.76 (5H, m), 5.20 (2H, s), 6.33 (1H, d, J=3Hz), 7.00 (1H, d, J=8Hz), 7.10-7.50 (9H, m), 7.69 (1H, s), 7.84 (1H, s), 8.32 (1H, s), 8.52 (1H, s)

Example 32

N-(1-Benzyloxycarbonyl-1,2,3,4-tetrahydroquinolin-5-yl)-N'-(1-methylindol-5-yl)urea was prepared in a similar manner to that of Example 13.

mp : 147-152°C

IR (Nujol) : 1700, 1630 cm^{-1}

NMR (DMSO-d_6, δ) : 1.80-2.00 (2H, m), 2.65 (2H, t, J=7Hz), 3.60-3.80 (5H, m), 5.19 (2H, s), 6.33 (1H, d, J=3Hz), 6.90-7.50 (10H, m), 7.60 (1H, d, J=7Hz), 7.71 (1H, d, J=2Hz), 7.84 (1H, s), 8.83 (1H, s)

Example 33

N-(2,3-Dihydrobenzo[b]furan-7-yl)-N'-(3-phthalimidomethylphenyl)urea was prepared in a similar manner to that of Example 13.

IR (Nujol) : 3260, 1740, 1700, 1640 cm^{-1}

NMR (DMSO-d_6, δ) : 3.21 (2H, t, J=8.6Hz), 4.60 (2H, t, J=8.7Hz), 4.74 (2H, s), 6.71-7.03 (3H, m), 7.19-7.42 (3H, m), 7.66-8.10 (5H, m), 8.67 (1H, s), 9.13 (1H, s)

MASS : 414 (M+1)

Example 34

To a solution of N-(benzyloxycarbonyl)-N-(4-methoxybenzyl)-3-nitrobenzylamine (1.5 g) in ethanol (20 ml), were added ferric chloride (50 mg), active carbon (500 mg), and hydrazine monohydrate (2 ml). This mixture was stirred at 70°C for 2 hours, filtered, and evaporated. The residue was dissolved in chloroform and washed with water, dried over magnesium sulfate, filtered, and evaporated. By using this amine, the following compound was obtained according to a similar manner to that of Example 13. N-(1-Methylindol-5-yl)-N'-[3-[N-benzyloxycarbonyl-N-(4-methoxybenzyl)-aminomethyl]phenyl]urea.

IR (Nujol) : 3300, 1700, 1610, 1560 cm^{-1}

NMR (DMSO-d_6, δ) : 3.74 (3H, s), 3.76 (3H, s), 4.36

(4H, s), 5.18 (2H, s), 6.34 (1H, d, J=2.9Hz), 6.80-6.96 (3H, m), 7.13-7.36 (13H, m), 7.70 (1H, s), 8.41 (1H, s), 8.61 (1H, s)

MASS : 549 (M+1)

Example 35

N-(1-Methylindol-5-yl)-N'-[3-[N-benzyloxycarbonyl-N-(4-methylbenzyl)aminomethyl]phenyl]urea was prepared in a similar manner to that of Example 34.

IR (Nujol) : 3260, 1690, 1610, 1540 cm^{-1}

NMR (DMSO-d_6, δ) : 2.29 (3H, s), 3.76 (3H, s), 4.37 (4H, s), 5.18 (2H, s), 6.34 (1H, s, J=2.9Hz), 6.79 (1H, s), 7.13-7.36 (15H, m), 7.70 (1H, s), 8.42 (1H, s), 8.63 (1H, s)

Example 36

To a suspension of 1-methylindole-5-carboxylic acid (1.0 g) in benzene were added triethylamine (0.80 ml) and diphenylphosphoryl azide (1.23 ml). The mixture was refluxed for 3 hours. After being cooled, 4-cyanoaniline (1.35 g) was added and refluxed for 7 hours. The reaction mixture was partitioned between water and ethyl acetate. Precipitates were collected, washed with water, and dried to give N-(4-cyanophenyl)-N'-(1-methylindol-5-yl)urea (1.11 g). From the ethyl acetate layer, another 0.41 g of N-(4-cyanophenyl)-N'-(1-methylindol-5-yl)urea was obtained.

mp : 238-240°C

IR (Nujol) : 2315, 1695, 1640 cm^{-1}

NMR (DMSO-d_6, δ) : 3.76 (3H, s), 6.36 (1H, d, J=3Hz), 7.15 (1H, dd, J=8Hz, 2Hz), 7.28 (1H, d, J=3Hz), 7.35 (1H, d, J=9Hz), 7.60-7.80 (5H, m), 8.63 (1H, s), 9.11 (1H, s)

MASS : 291 ($M+1^{\oplus}$)

Exampl 37

N-(3-Cyanophenyl)-N'-(4-dimethylaminophenyl)urea was prepared in a similar manner to that of Example 36.

IR (Nujol) : 3310, 2200, 1640, 1600 cm^{-1}

NMR (DMSO-d_6, δ) : 2.84 (6H, s), 6.68 (1H, s), 6.73 (1H, s), 7.25 (1H, s), 7.29 (1H, s), 7.37-7.67 (3H, m), 8.32 (1H, s), 8.47 (1H, s), 8.89 (1H, s)

MASS : 281 (M+1)

Example 38

N-(3-Cyanophenyl)-N'-(2,3-dihydrobenzo[b]furan-7-yl)urea was prepared in a similar manner to that of Example 36.

IR (Nujol) : 2200, 1650, 1600 cm^{-1}

NMR (DMSO-d_6, δ) : 3.23 (2H, t, J=8.8Hz), 4.62 (2H, t, J=8.7Hz), 6.74-6.92 (2H, m), 7.40-7.64 (3H, m), 7.80 (1H, d, J=7.3Hz), 7.98 (1H, s), 8.30 (1H, s), 9.41 (1H, s)

MASS : 280 (M+1)

Example 39

N-(1-Methylindol-5-yl)-N'-(4-thiocarbamoylphenyl)urea was prepared in a similar manner to that of Example 2.

IR (Nujol) : 1650, 1620, 1590 cm^{-1}

NMR (DMSO-d_6, δ) : 3.76 (3H, s), 6.35 (1H, d, J=3Hz), 7.15 (1H, dd, J=7Hz, 2Hz), 7.27 (1H, d, J=3Hz), 7.35 (1H, d, J=9Hz), 7.44 (2H, d, J=12Hz), 7.70 (1H, d, J=2Hz), 7.80-8.00 (3H, m), 8.55 (1H, s), 8.91 (1H, s), 9.30 (1H, br s), 9.61 (1H, br s)

Example 40

N-(1-Methylindol-5-yl)-N'-[4-[methylthio(imino)methyl]-phenyl]urea hydroiodide was prepared in a similar manner to that of Example 3.

mp : 95-105°C

IR (Nujol) : 1645 cm^{-1}

NMR (DMSO-d_6, δ) : 2.83 (3H, s), 3.77 (3H, s), 6.36

(1H, d, J=3Hz), 7.17 (1H, dd, J=9Hz, 2Hz), 7.30 (1H, d, J=3Hz), 7.37 (1H, d, J=9Hz), 7.70-7.80 (3H, m), 7.80-8.10 (2H, m), 8.73 (1H, s), 9.34 (1H, s)

MASS : 339 ($M+1^{\oplus}$), 291 ($M-48(CH_3SH)+1)^{\oplus}$

Example 41

N-(3-Thiocarbamoylphenyl)-N'-(4-dimethylaminophenyl)urea was prepared in a similar manner to that of Example 2.

IR (Nujol) : 3280, 1620 cm^{-1}

NMR (DMSO-d_6, δ) : 2.83 (6H, s), 6.67 (1H, s), 6.72 (1H, s), 7.24-7.39 (4H, m), 7.61-7.66 (1H, m), 7.91 (1H, s), 8.28 (1H, s), 8.71 (1H, s), 9.46 (1H, s), 9.84 (1H, s)

MASS : 315 (M+1)

Example 42

N-[3-[Methylthio(imino)methyl]phenyl]-N'-(4-dimethylaminophenyl)urea hydroiodide was prepared in a similar manner to that of Example 3.

IR (Nujol) : 1670 cm^{-1}

NMR (DMSO-d_6, δ) : 2.86 (3H, s), 3.61 (3H, s), 7.25-7.76 (5H, m), 7.89 (1H, s), 8.16 (1H, s), 9.25 (1H, s), 9.29 (1H, s)

MASS : 329 (M+1)

Example 43

N-[3-[Methylthio(imino)methyl]phenyl]-N'-(2,3-dihydrobenzo[b]furan-7-yl)urea hydroiodide was prepared in similar manners to those of Example 2, and then Example 3.

IR (Nujol) : 1690, 1600 cm^{-1}

NMR (DMSO-d_6, δ) : 2.41 (3H, s), 3.23 (2H, t, J=8.8Hz), 4.62 (2H, t, J=8.7Hz), 6.73-6.90 (2H, m), 7.25-7.51 (3H, m), 7.82-7.86 (1H, s), 8.16-8.20 (1H, m), 9.28 (1H, s), 10.19 (1H, s), 10.36 (1H, s)

MASS : 328 (M+1)

Example 44

N-(4-Amidinophenyl)-N'-(1-methylindol-5-yl)urea hydroiodide was prepared in a similar manner to that of Example 5.

mp : 167-172°C

IR (Nujol) : 1650, 1630 cm^{-1}

NMR (DMSO-d_6, δ) : 3.77 (3H, s), 6.35 (1H, d, J=3Hz), 7.17 (1H, dd, J=9Hz, 2Hz), 7.28 (1H, d, J=3Hz), 7.34 (1H, d, J=9Hz), 7.60-7.90 (5H, m), 8.60-9.40 (6H, m)

MASS : 308 ($M+1^{\oplus}$)

Example 45

N-(1-Methylindol-5-yl)-N'-[4-(phenylamidino)phenyl]urea hydroiodide was prepared in a similar manner to that of Example 6.

mp : >280°C

IR (Nujol) : 1685, 1650 cm^{-1}

NMR (DMSO-d_6, δ) : 3.77 (3H, s), 6.36 (1H, d, J=3Hz), 7.15 (1H, dd, J=9Hz, 2Hz), 7.29 (1H, d, J=3Hz), 7.30-7.65 (6H, m), 7.70-7.75 (3H, m), 7.86 (2H, d, J=9Hz), 8.66 (1H, s), 9.14 (1H, s)

MASS : 384 ($M+1^{\oplus}$)

Example 46

N-[4-(Benzylamidino)phenyl]-N'-(1-methylindol-5-yl)urea hydroiodide was prepared in a similar manner to that of Example 6.

mp : 155-165°C

IR (Nujol) : 1650 cm^{-1}

NMR (DMSO-d_6, δ) : 3.76 (3H, s), 4.65 (2H, s), 6.35 (1H, d, J=3Hz), 7.10-8.10 (16H, m), 9.34 (1H, s), 9.86 (1H, s)

MASS : 398 ($M+1^{\oplus}$)

Example 47

N-(1-Methylindol-5-yl)-N'-[3-(3-phenylpropyl)-amidinophenyl]urea hydroiodide was prepared in a similar

manner to that of Example 6.

IR (Nujol) : 3250, 1650, 1580 cm^{-1}

NMR (DMSO-d_6, δ): 1.70-2.00 (4H, m), 2.70 (2H, m), 3.40 (2H, t, J=7Hz), 3.75 (3H, s), 6.32 (1H, d, J=3Hz), 7.15-7.40 (11H, m), 7.47 (1H, t, J=9Hz), 7.75 (2H, m), 8.06 (1H, s), 9.94 (1H, s), 10.40 (1H, s)

MASS : 426 (M^++1)

Example 48

N-(1-Methylindol-5-yl)-N'-[3-(2-phenylethyl)-amidinophenyl]urea hydroiodide was prepared in a similar manner to that of Example 6.

IR (Nujol) : 3250, 1655, 1580, 1540 cm^{-1}

NMR (DMSO-d_6, δ) : 2.97 (2H, t, J=8Hz), 3.36 (2H, t, J=8Hz), 3.76 (3H, s), 6.35 (1H, d, J=3Hz), 7.10-7.40 (12H, m), 7.48 (1H, t, J=8Hz), 7.64 (1H, d, J=9Hz), 7.77 (1H, s), 7.85 (1H, s), 8.92 (1H, s), 9.28 (1H, s)

MASS : 412 (M^++1)

Example 49

N-(Benzo[b]furan-5-yl)-N'-[3-(phenylamidino)phenyl]urea hydroiodide was prepared in a similar manner to that of Example 6.

IR (Nujol) : 3500-3000, 1650, 1590, 1540 cm^{-1}

NMR (DMSO-d_6, δ) : 6.60 (1H, m), 6.90-7.00 (1H, m), 7.20-7.60 (10H, m), 7.70 (1H, m), 7.85 (1H, d, J=2Hz), 7.95 (1H, d, J=2Hz), 8.13 (1H, m), 8.83 (1H, s), 9.04 (1H, s)

MASS : 371 (M^++1)

Example 50

N-[3-(Phenylamidino)phenyl]-N'-(4-dimethylaminophenyl)-urea hydroiodide was prepared in a similar manner to that of Example 6.

mp : 166-172°C

IR (Nujol) : 1650 cm^{-1}

NMR (DMSO-d_6, δ) : 3.59 (6H, s), 7.36-7.77 (10H, m), 7.88-7.92 (2H, m), 8.10 (1H, s), 9.06 (1H, s), 9.22-9.24 (2H, m), 9.85 (1H, s), 11.43 (1H, s)

MASS : 374 (M+1)

Example 51

N-[3-(Phenylamidino)phenyl]-N'-(2,3-dihydrobenzo[b]-furan-7-yl)urea hydroiodide was prepared in a similar manner to that of Example 6.

mp : 97-105°C

IR (Nujol) : 1660 cm^{-1}

NMR (DMSO-d_6, δ) : 3.23 (2H, t, J=8.6Hz), 4.61 (2H, t, J=8.6Hz), 6.73-7.06 (5H, m), 7.30-7.62 (5H, m), 7.85 (1H, d, J=7.8Hz), 7.99 (1H, s), 8.21 (1H, s), 9.28 (1H, s)

MASS : 373 (M+1)

Example 52

A mixture of N-(1-methylindol-5-yl)-N'-(3-phthalimidomethylphenyl)urea (420 mg) and hydrazine monohydrate (150 mg) in ethanol (100 ml) was stirred at 70°C for 5 hours. After evaporation of the solvent, the residue was partitioned between ethyl acetate and 1N aqueous sodium hydroxide. The organic layer was washed with water, dried over magnesium sulfate, filtered, and evaporated. This residue was recrystallized from chloroform-hexane to give N-(1-methylindol-5-yl)-N'-(3-aminomethylphenyl)urea.

mp : 123-126°C

IR (Nujol) : 1610 cm^{-1}

NMR (DMSO-d_6, δ) : 1.81 (2H, s), 3.75 (3H, s), 6.32 (1H, d, J=2.9Hz), 6.90 (1H, d, J=7.5Hz), 7.14-7.48 (8H, m), 7.74 (1H, s), 9.39 (1H, s), 9.51 (1H, s)

MASS : 295 (M+1)

Example 53

N-(4-Aminomethylphenyl)-N'-(1-methylindol-5-yl)urea was prepared in a similar manner to that of Example 52.

mp : 173-175°C

IR (Nujol) : 1635 cm^{-1}

NMR (DMSO-d_6, δ) : 3.65 (2H, s), 3.75 (3H, s), 6.33 (1H, d, J=3Hz), 7.10-7.45 (7H, m), 7.68 (1H, d, J=2Hz), 8.44 (1H, s), 8.54 (1H, s)

MASS (FAB) : 295 ($M+1^{\oplus}$)

Example 54

N-(2,3-Dihydrobenzo[b]furan-7-yl)-N'-(3-aminomethylphenyl)urea was prepared in a similar manner to that of Example 52.

mp : 151-153°C

IR (Nujol) : 3240, 1650, 1590 cm^{-1}

NMR (DMSO-d_6, δ) : 3.22 (2H, t, J=8.6Hz), 4.02 (2H, s), 4.61 (2H, t, J=8.7Hz), 6.72-6.95 (3H, m), 7.16-7.37 (3H, m), 7.86 (1H, d, J=7.1Hz), 8.17 (1H, s), 9.07 (1H, s)

MASS : 284 (M+1)

Example 55

To a solution of 7-nitrobenzo[b]furan (1.23 g) in ethanol (100 ml) were added hydrazine hydrate (660 µl), ferric chloride (20 mg) and active carbon (200 mg). The mixture was stirred at 70°C for 2 hours, filtered, and evaporated. The residue was dissolved in ethyl acetate, and washed with water. The organic layer was dried over magnesium sulfate, filtered, and evaporated to give 7-aminobenzo[b]furan. By using this, the following compound was obtained according to similar manners to those of Example 13, and then Example 52.

N-(3-Aminomethylphenyl)-N'-(benzo[b]furan-7-yl)urea

IR (Nujol) : 1680 cm^{-1}

NMR (DMSO-d_6, δ) : 3.71 (2H, s), 6.95-6.98 (2H, m),

7.13-7.43 (5H, m), 7.98-8.06 (2H, m), 8.87 (1H, s), 9.15 (1H, s)

MASS : 282 (M+1)

Example 56

To a mixture of N-(1-methylindol-5-yl)-N'-[3-[(3-benzyloxycarbonylguanidino)methyl]phenyl]urea (100 mg), tetrahydrofuran (10 ml) and methanol (10 ml), 10% palladium on carbon (30 mg) was added. This mixture was hydrogenated at 1 atm at ambient temperature for 1 hour. The mixture was filtered through celite and evaporated. The resulting oil was triturated with diisopropyl ether to give N-(1-methylindol-5-yl)-N'-[3-(guanidinomethyl)phenyl]urea.

IR (Nujol) : 1650, 1540 cm^{-1}

NMR (DMSO-d_6, δ) : 3.75 (3H, s), 4.33 (2H, s), 6.33 (1H, d, J=2.9Hz), 6.86 (1H, d, J=7.4Hz), 7.14-7.73 (9H, m)

MASS : 337 (M+1)

Example 57

To a mixture of N-(1-methylindol-5-yl)-N'-[3-[N-benzyloxycarbonyl-N-(4-methoxybenzyl)aminomethyl]phenyl]urea (1 g) in methanol (15 ml) and tetrahydrofuran (15 ml) were added 10% palladium on carbon. This mixture was hydrogenated at 1 atm at ambient temperature for 1 hour, filtered and evaporated. The resulting oil was triturated with diisopropyl ether to give N-(1-methylindol-5-yl)-N'-[3-[(4-methoxybenzyl)aminomethyl]phenyl]urea.

mp : 78-80°C

IR (Nujol) : 1610, 1540 cm^{-1}

NMR (DMSO-d_6, δ) : 2.80-3.00 (1H, m), 3.63 (4H, s), 3.73 (3H, s), 3.75 (3H, s), 6.34 (1H, s), 6.86-6.90 (3H, m), 7.10-7.50 (6H, m), 7.69 (1H, s), 8.41 (1H, s), 8.55 (1H, s)

MASS : 415 (M+1)

Example 58

N-(1-Methylindol-5-yl)-N'-[3-[(4-methylbenzyl)-aminomethyl]phenyl]urea was prepared in a similar manner to that of Example 57.

mp : 92-94°C

IR (Nujol) : 1610, 1540 cm^{-1}

NMR (DMSO-d_6, δ) : 2.28 (3H, s), 3.64-3.65 (4H, m), 3.75 (3H, s), 6.34 (1H, d, J=2.9Hz), 6.91 (1H, d, J=6.9Hz), 7.10-7.43 (11H, m), 7.69 (1H, d, J=1.5Hz), 8.41 (1H, s), 8.56 (1H, s)

MASS : 533 (M+1)

Example 59

N-(1-Methylindol-5-yl)-N'-[3-(methylaminomethyl)-phenyl]urea maleate was prepared in similar manners to those of Example 34, and then Example 57.

mp : 172-175°C

IR (Nujol) : 3300, 1630, 1610 cm^{-1}

NMR (DMSO-d_6, δ) : 2.56 (3H, s), 3.76 (3H, s), 4.10 (2H, s), 6.04 (2H, s), 6.34 (1H, d, J=2.6Hz), 7.05 (1H, d, J=6.7Hz), 7.15 (1H, dd, J=8.7Hz, 1.9Hz), 7.27-7.42 (4H, m), 7.70-7.71 (2H, m), 8.57 (1H, s), 8.6-8.9 (3H, m)

MASS : 309 (M+1)

Example 60

N-(1-Methylindol-5-yl)-N'-(1,2,3,4-tetrahydroisoquinolin-7-yl)urea was prepared in a similar manner to that of Example 57.

mp : 174-177°C

IR (Nujol) : 1600, 1640 cm^{-1}

NMR (DMSO-d_6, δ) : 2.63 (2H, t, J=6Hz), 2.96 (2H, t, J=6Hz), 3.75 (3H, s), 3.84 (2H, s), 6.33 (1H, d, J=3Hz), 6.95 (1H, d, J=8Hz), 7.10-7.40 (5H, m), 7.68 (1H, d, J=2Hz), 8.45 (1H, s), 8.48 (1H, s)

MASS : 321 ($M+1^{\oplus}$)

Example 61

N-(1-Methylindol-5-yl)-N'-(1,2,3,4-tetrahydroisoquinolin-5-yl)urea was prepared in a similar manner to that of Example 57.

mp : 167-169°C

IR (Nujol) : 1625 cm^{-1}

NMR (DMSO-d_6, δ) : 2.55 (2H, t, J=6Hz), 3.03 (2H, t, J=6Hz), 3.76 (3H, s), 3.84 (2H, s), 6.34 (1H, d, J=3Hz), 6.70 (1H, d, J=7Hz), 7.00-7.20 (2H, m), 7.26 (1H, d, J=3Hz), 7.34 (1H, d, J=9Hz), 7.70-7.80 (3H, m), 8.86 (1H, s)

MASS : 321 ($M+1^{\oplus}$)

Example 62

N-(1-Methylindol-5-yl)-N'-(1,2,3,4-tetrahydroquinolin-5-yl)urea was prepared in a similar manner to that of Example 57.

mp : 180-185°C

IR (Nujol) : 1620, 1600 cm^{-1}

NMR (DMSO-d_6, δ) : 1.83 (2H, br s), 2.51 (2H, br s), 3.12 (2H, br s), 3.75 (3H, s), 5.59 (1H, br s), 6.17 (1H, d, J=8Hz), 6.33 (1H, d, J=3Hz), 6.70-7.40 (5H, m), 7.57 (1H, s), 7.69 (1H, s), 8.70 (1H, s)

MASS : 321 ($M+1^{\oplus}$)

Example 63

N-(1-Methylindol-5-yl)-N'-(1,2,3,4-tetrahydroquinolin-7-yl)urea was prepared in a similar manner to that of Example 57.

mp : 225-230°C

IR (Nujol) : 1640, 1620 cm^{-1}

NMR (DMSO-d_6, δ) : 1.60-1.90 (2H, m), 2.40-2.65 (2H, m), 3.10-3.20 (2H, m), 3.75 (3H, s), 5.60 (1H, br s), 6.32 (1H, d, J=3Hz), 6.45 (1H, dd, J=8Hz, 2Hz), 6.60-6.75 (2H, m), 7.11 (1H, dd, J=9Hz, 2Hz), 7.25 (1H, d, J=3Hz), 7.31 (1H, d, J=9Hz), 7.66 (1H, d,

J=2Hz), 8.16 (1H, s), 8.26 (1H, s)
MASS : 321 ($M+1^{\oplus}$)

Example 64

To a solution of N-[3-(1-formylaminoethyl)phenyl]-N'-(1-methylindol-5-yl)urea (0.30 g) in ethanol (10 ml) was added 1N-aqueous sodium hydroxide (2.7 ml). The mixture was refluxed for 9 hours. After evaporation, resulting mass was partitioned between water and ethyl acetate. Organic layer was dried over sodium sulfate, and chromatographed on silica gel eluted by chloroform-methanol-aqueous ammonia (10:1:0 to 10:1:0.05) to give N-[3-(1-aminoethyl)phenyl]-N'-[1-methylindol-5-yl]urea (0.19 g).

mp : 90-110°C (amorphous)
IR (Nujol) : 1650 cm^{-1}
NMR (DMSO-d_6, δ) : 1.29 (3H, d, J=6Hz), 3.75 (3H, s), 4.03 (1H, q, J=6Hz), 6.33 (1H, d, J=3Hz), 7.10-7.40 (5H, m), 7.47 (1H, s), 7.70 (1H, s), 8.56 (1H, s), 8.70 (1H, s)
MASS : 309 ($M+1^{\oplus}$), 617 ($2M+1^{\oplus}$)

Example 65

N-(8-Amino-5,6,7,8-tetrahydro-2-naphthyl)-N'-(1-methylindol-5-yl)urea was prepared in a similar manner to that of Example 64.

mp : 175-180°C
IR (Nujol) : 1665, 1595 cm^{-1}
NMR (DMSO-d_6, δ) : 1.50-2.10 (4H, m), 2.45-2.70 (2H, m), 3.75 (3H, s), 4.00 (1H, br s), 6.32 (1H, d, J=3Hz), 6.98 (1H, d, J=8Hz), 7.14 (1H, dd, J=9Hz, 2Hz), 7.20-7.35 (3H, m), 7.52 (1H, d, J=2Hz), 7.70 (1H, d, J=2Hz), 8.69 (2H, s)
MASS : 318 ($M-NH_2$)$^{\oplus}$

Example 66

To a solution of N-[4-(aminomethyl)phenyl]-N'-(1-methylindol-5-yl)urea (0.10 g) in N,N-dimethylformamide (5 ml) was added [(methylthio)(imino)methyl]benzene hydroiodide

(95 mg). The mixture was stirred at 100°C for 5 hours. After being cooled, the mixture was poured into water, alkalized by aqueous sodium hydroxide to pH=12, and extracted with ethyl acetate. The extract was dried over sodium sulfate, evaporated, and chromatographed on silica gel eluted by chloroform-methanol-aqueous ammonia (9:1:0.1, V/V), to give N-[4-[[(imino)(phenyl)methyl]aminomethyl]phenyl]-N'-(1-methylindol-5-yl)urea (0.08 g).

mp : 120-130°C

IR (Nujol) : 1650, 1590 cm^{-1}

NMR (DMSO-d_6, δ) : 3.75 (3H, s), 4.36 (2H, s), 6.33 (1H, d, J=3Hz), 7.14 (1H, dd, J=9Hz, 2Hz), 7.20-7.50 (10H, m), 7.69 (1H, d, J=2Hz), 7.75-7.85 (2H, m), 8.53 (1H, br s), 8.67 (1H, br s)

MASS : 398 ($M+1^{\oplus}$)

Example 67

N-(1-Methylindol-5-yl)-N'-[3-[[(imino)(phenyl)methyl]-aminomethyl]phenyl]urea hydroiodide was prepared in a similar manner to that of Example 66.

mp : 144-147°C

IR (Nujol) : 1650 cm^{-1}

NMR (DMSO-d_6, δ) : 3.76 (3H, s), 4.67 (2H, s), 6.34 (1H, d, J=2.9Hz), 7.01 (1H, d, J=6.8Hz), 7.15 (1H, dd, J=8.7Hz, 1.9Hz), 7.2-7.4 (5H, m), 7.6-7.9 (9H, m), 8.55 (1H, s), 8.76 (1H, s), 9.1-9.7 (1H, m), 10-10.4 (1H, m)

MASS : 398 (M+1)

Example 68

N-[3-[1-[[(Imino)(phenyl)methyl]amino]ethyl]phenyl]-N'-[1-methylindol-5-yl]urea was prepared in a similar manner to that of Example 66.

mp : 110-125°C

IR (Nujol) : 1650, 1590 cm^{-1}

NMR (DMSO-d_6, δ) : 1.40 (3H, d, J=7Hz), 3.75 (3H, s),

4.70-4.80 (1H, m), 6.33 (1H, d, J=3Hz), 6.90 (2H, br s), 7.00-7.50 (10H, m), 7.69 (1H, d, J=2Hz), 7.75-7.85 (2H, m), 8.44 (1H, s), 8.61 (1H, s)

MASS : 412 ($M+1^{\oplus}$)

Example 69

N-(1-Methylindol-5-yl)-N'-[3-[[(1-methylindol-5-yl)(imino)methyl]aminomethyl]phenyl]urea hydroiodide was prepared in a similar manner to that of Example 66.

mp : 164-172°C

IR (Nujol) : 1640, 1580 cm^{-1}

NMR (DMSO-d_6, δ) : 3.76 (3H, s), 3.88 (3H, s), 4.69 (2H, s), 6.34 (1H, d, J=2.9Hz), 6.67 (1H, d, J=3.1Hz), 7.02 (1H, d, J=6.5Hz), 7.15 (1H, dd, J=8.8Hz, 1.9Hz), 7.27-7.36 (4H, m), 7.56-7.72 (5H, m), 8.15 (1H, s), 8.51 (1H, s), 8.73 (1H, s), 9.00 (1H, s), 9.41 (1H, s), 10.08 (1H, s)

MASS : 451 (M+1)

Example 70

N-[3-[[(Imino)(phenyl)methyl]aminomethyl]phenyl]-N'-(benzo[b]furan-7-yl)urea hydrochloride was prepared in a similar manner to that of Example 66.

mp : 132-165°C

IR (Nujol) : 1680, 1600 cm^{-1}

NMR (DMSO-d_6, δ) : 4.71 (2H, d, J=5.9Hz), 6.98-7.48 (6H, m), 7.60-8.05 (8H, m), 9.12 (1H, s), 9.36 (1H, s), 9.66 (1H, s), 9.80 (1H, s), 10.39 (1H, s)

MASS : 385 (M+1)

Example 71

N-[3-[[(Imino)(phenyl)methyl]aminomethyl]phenyl]-N'-(2,3-dihydrobenzo[b]furan-7-yl)urea hydrochloride was prepared in a similar manner to that of Example 66.

mp : 132-165°C

IR (Nujol) : 1660, 1590 cm^{-1}

NMR (DMSO-d_6, δ) : 3.22 (2H, t, J=8.7Hz), 4.59 (2H, t, J=8.7Hz), 4.71 (2H, s), 6.72-6.89 (2H, m), 7.03 (1H, d, J=7.4Hz), 7.27-7.43 (2H, m), 7.59-7.86 (7H, m), 8.33 (1H, d, J=6.3Hz), 9.39 (1H, s), 9.58 (1H, s), 9.67 (1H, s), 10.40 (1H, s)

MASS : 387 (M+1)

Example 72

A mixture of N-(1-methylindol-5-yl)-N'-[3-(aminomethyl)phenyl]urea (280 mg) and N-benzyloxycarbonyl-S-methylisothiourea (230 mg) in isopropyl alcohol (15 ml) was heated at 80°C overnight. After evaporation of the solvent, the residue was dissolved in chloroform, washed with 1N aqueous sodium hydroxide solution twice, dried over magnesium sulfate, filtered, and evaporated. The residue was chromatographed on silica gel (2% methanol in chloroform) to give N-(1-methylindol-5-yl)-N'-[3-[(3-benzyloxycarbonyl-guanidino)methyl]phenyl]urea.

IR (Nujol) : 3410, 1650, 1610 cm^{-1}

NMR (DMSO-d_6, δ) : 3.75 (3H, s), 4.3-4.4 (2H, m), 4.97 (2H, s), 6.33-6.34 (1H, m), 6.83-6.87 (1H, m), 7.11-7.68 (14H, m), 8.38 (1H, s), 8.59 (1H, s)

Example 73

A mixture of N-(1-methylindol-5-yl)-N'-[3-(aminomethyl)phenyl]urea (500 mg), benzyl bromide (318 mg) and potassium carbonate (257 mg) in N,N-dimethylformamide (15 ml) was stirred at 100°C for 3 hours. This solution was partitioned between ethyl acetate and water. The organic layer was washed with water, dried over magnesium sulfate, filtered, and evaporated. The residue was chromatographed on silica gel (chloroform), triturated with ether to give N-(1-methylindol-5-yl)-N'-[3-(benzylaminomethyl)phenyl]urea.

mp : 119-123°C

IR (Nujol) : 1610 cm^{-1}

NMR (DMSO-d_6, δ) : 3.66 (2H, s), 3.71 (2H, s), 3.75 (3H, s), 6.34 (1H, d, J=2.9Hz), 6.93 (1H, d, J=7.3Hz), 7.13-7.44 (12H, m), 7.70 (1H, s), 8.44 (1H, s), 8.59 (1H, s)

MASS : 385 (M+1)

Example 74

N-[3-(Benzylaminomethyl)phenyl]-N'-(benzo[b]furan-7-yl)-urea was prepared in a similar manner to that of Example 73.

mp : 78-82°C

IR (Nujol) : 1620 cm^{-1}

NMR (DMSO-d_6, δ) : 3.70 (2H, s), 3.73 (2H, s), 6.99-7.47 (12H, m), 7.96-8.05 (2H, m), 8.83 (1H, s), 9.15 (1H, s)

MASS : 372 (M+1)

Example 75

N-[3-(Benzylaminomethyl)phenyl]-N'-(2,3-dihydrobenzo[b]furan-7-yl)urea hydrochloride was prepared in a similar manner to that of Example 73.

mp : 106-112°C

NMR (DMSO-d_6, δ) : 3.22 (2H, t, J=8.6Hz), 4.09-4.15 (4H, m), 4.59 (2H, t, J=8.6Hz), 6.72-6.89 (2H, m), 7.17 (1H, d, J=7.4Hz), 7.29-7.64 (8H, m), 7.82 (1H, d, J=7.7Hz), 8.37 (1H, s), 9.54 (1H, s), 9.75 (2H, s)

MASS : 387 (M+1)

Example 76

N-(1-Methylindol-5-yl)-N'-[3-[(2-fluorobenzylamino)-methyl]phenyl]urea was prepared in a similar manner to that of Example 73.

mp : 109-112°C

IR (Nujol) : 1610, 1540 cm^{-1}

NMR (DMSO-d_6, δ) : 3.69 (4H, s), 3.75 (3H, s), 6.34

(1H, d, J=2.9Hz), 6.93 (1H, d, J=7.4Hz), 7.11-7.55 (11H, m), 7.68 (1H, s), 8.41 (1H, s), 8.55 (1H, s)

MASS : 403 (M+1)

Example 77

N-(1-Methylindol-5-yl)-N'-[3-[(3-chlorobenzylamino)-methyl]phenyl]urea was prepared in a similar manner to that of Example 73.

mp : 124-125°C

IR (Nujol) : 1610, 1540 cm^{-1}

NMR (DMSO-d_6, δ) : 2.75 (1H, s), 3.65 (2H, s), 3.70 (2H, s), 3.75 (3H, s), 6.34 (1H, d, J=2.8Hz), 6.92 (1H, d, J=7.4Hz), 7.12-7.45 (11H, m), 7.70 (1H, d, J=1.7Hz), 8.40 (1H, s), 8.55 (1H, s)

MASS : 419 (M+1)

Example 78

N-(1-Methylindol-5-yl)-N'-[3-[(2-chlorobenzylamino)-methyl]phenyl]urea was prepared in a similar manner to that of Example 73.

mp : 126-136°C

IR (Nujol) : 1610, 1540 cm^{-1}

NMR (DMSO-d_6, δ) : 2.69 (1H, s), 3.71 (2H, s), 3.75 (3H, s), 3.78 (2H, s), 6.34 (1H, d, J=2.8Hz), 6.95 (1H, d, J=7.3Hz), 7.12-7.44 (9H, m), 7.59 (1H, d, J=6.2Hz), 7.69 (1H, s), 8.40 (1H, s), 8.54 (1H, s)

MASS : 419 (M+1)

Example 79

N-(1-Methylindol-5-yl)-N'-[3-[(4-chlorobenzylamino)-methyl]phenyl]urea was prepared in a similar manner to that of Example 73.

mp : 114-119°C

IR (Nujol) : 1610 cm^{-1}

NMR (DMSO-d_6, δ) : 3.64 (2H, s), 3.68 (2H, s), 3.75

(3H, s), 6.34 (1H, d, J=2.9Hz), 7.34 (1H, d, J=7.3Hz), 7.12-7.43 (11H, m), 7.68 (1H, s), 8.40 (1H, s), 8.54 (1H, s)

MASS : 419 (M+1)

Example 80

N-(1-Methylindol-5-yl)-N'-[3-[(4-chlorobenzylamino)-methyl]phenyl]urea was prepared in a similar manner to that of Example 73.

mp : 141-144°C

IR (Nujol) : 1610, 1540 cm^{-1}

NMR (DMSO-d_6, δ) : 3.66 (2H, s), 3.69 (2H, s), 3.75 (3H, s), 6.34 (1H, d, J=2.6Hz), 6.93 (1H, d, J=7.6Hz), 7.10-7.44 (11H, m), 7.69 (1H, s), 8.44 (1H, s), 8.58 (1H, s)

MASS : 403 (M+1)

Example 81

N-(1-Methylindol-5-yl)-N'-[3-[(3,5-dichlorobenzylamino)-methyl]phenyl]urea was prepared in a similar manner to that of Example 73.

mp : 155-159°C

IR (Nujol) : 1610, 1570 cm^{-1}

NMR (DMSO-d_6, δ) : 2.87 (1H, s), 3.64 (2H, s), 3.70 (2H, s), 3.75 (3H, s), 6.33 (1H, d, J=2.8Hz), 6.97 (1H, d, J=7.3Hz), 7.13-7.44 (9H, m), 7.71 (1H, s), 8.41 (1H, s), 8.55 (1H, s)

MASS : 453 (M)

Example 82

N-(1-Methylindol-5-yl)-N'-[3-[(N-methyl-N-benzylamino)-methyl]phenyl]urea was prepared in a similar manner to that of Example 73.

mp : 78-80°C

IR (Nujol) : 1610, 1540 cm^{-1}

NMR (DMSO-d_6, δ) : 2.10 (3H, s), 3.46 (2H, s), 3.50 (2H, s), 3.76 (3H, s), 6.34 (1H, d, J=2.9Hz), 6.92 (1H, d, J=7.4Hz), 7.13-7.70 (12H, m), 8.61 (1H, s), 8.77 (1H, s)

MASS : 399 (M+1)

Example 83

N-(4-(Dibenzylaminomethyl)phenyl]-N'-[1-methylindol-5-yl]urea was prepared in a similar manner to that of Example 73.

mp : 181-183°C

IR (Nujol) : 1640 cm^{-1}

NMR (DMSO-d_6, δ) : 3.44 (2H, s), 3.49 (4H, s), 3.75 (3H, s), 6.33 (2H, d, J=3Hz), 7.13 (1H, dd, J=9Hz, 2Hz), 7.20-7.50 (16H, m), 7.68 (1H, d, J=2Hz), 8.41 (1H, br s), 8.54 (1H, br s)

MASS : 475 ($M+1^{\oplus}$)

Example 84

To a suspension of N-[4-(aminomethyl)phenyl]-N'-[1-methylindol-5-yl]urea (0.15 g) in toluene (5 ml) was added benzaldehyde (0.052 ml). The mixture was refluxed under nitrogen atmosphere for 4 hours. After evaporation, the residue was suspended in ethanol (15 ml), and sodium borohydride (57.9 mg) was added. The mixture was stirred at 50°C for 2 hours. After evaporation, the residue was partitioned between water and chloroform. The chloroform layer was dried over sodium sulfate, and chromatographed on silica gel eluted by chloroform-methanol (0-5%, V/V) to give N-[4-(benzylaminomethyl)phenyl]-N'-[1-methylindol-5-yl]urea (0.11 g).

mp : 125-130°C

IR (Nujol) : 1640 cm^{-1}

NMR (DMSO-d_6, δ) : 3.62 (2H, s), 3.68 (2H, s), 3.75 (3H, s), 6.33 (1H, d, J=3Hz), 7.10-7.45 (12H, m), 7.68 (1H, d, J=2Hz), 8.40 (1H, br s), 8.51 (1H,

br s)
MASS : 385 ($M+1^{\oplus}$), 278 ($M-phCH_2NH^{\oplus}$)

Example 85

N-(1-Methylindol-5-yl)-N'-[3-[(2,6-dimethoxybenzyl)-aminomethyl]phenyl]urea was prepared in a similar manner to that of Example 84.

mp : 168-171°C

IR (Nujol) : 1610, 1590, 1540 cm^{-1}

NMR (DMSO-d_6, δ) : 3.34 (4H, s), 3.75 (3H, s), 3.77 (7H, s), 6.34 (1H, d, J=2.9Hz), 6.64 (1H, s), 6.68 (1H, s), 6.87 (1H, d, J=7.4Hz), 7.12-7.31 (6H, m), 7.47 (1H, s), 7.69 (1H, d, J=1.7Hz), 8.50 (1H, s), 8.64 (1H, s)

MASS : 445 (M+1)

Example 86

N-(1-Methylindol-5-yl)-N'-[3-(3-pyridylmethylaminomethyl)phenyl]urea was prepared in a similar manner to that of Example 84.

mp : 115-122°C

IR (Nujol) : 1650, 1600, 1540 cm^{-1}

NMR (DMSO-d_6, δ) : 2.84 (1H, s), 3.66 (2H, s), 3.71 (2H, s), 3.75 (3H, s), 6.34 (1H, d, J=2.9Hz), 6.93 (1H, d, J=7.3Hz), 7.13-7.44 (7H, m), 7.70-7.80 (2H, m), 8.41-8.55 (4H, m)

MASS : 386 (M+1)

Example 87

N-(1-Methylindol-5-yl)-N'-[3-[(2,5-difluorobenzyl)-aminomethyl]phenyl]urea was prepared in a similar manner to that of Example 84.

mp : 121-130°C

IR (Nujol) : 1610, 1540 cm^{-1}

NMR (DMSO-d_6, δ) : 2.72 (1H, s), 3.68 (2H, s), 3.72 (2H, s), 3.75 (3H, s), 6.34 (1H, d, J=2.9Hz), 6.93

(1H, d, J=7.4Hz), 7.12-7.44 (9H, m), 7.69 (1H, s), 8.40 (1H, s), 8.55 (1H, s)

MASS : 421 (M+1)

Example 88

N-(1-Methylindol-5-yl)-N'-[3-[(2-methoxybenzyl)-aminomethyl]phenyl]urea was prepared in a similar manner to that of Example 84.

mp : 124-140°C

IR (Nujol) : 1610, 1540 cm^{-1}

NMR (DMSO-d_6, δ) : 3.68-3.69 (4H, m), 3.75 (3H, s), 3.77 (3H, s), 6.33 (1H, d, J=2.9Hz), 6.89-6.98 (3H, m), 7.12-7.45 (8H, m), 7.69 (1H, d, J=1.7Hz), 8.42 (1H, s), 8.57 (1H, s)

MASS : 415 (M+1)

Example 89

N-(1-Methylindol-5-yl)-N'-[3-[(1-naphthyl)-methylaminomethyl]phenyl]urea was prepared in a similar manner to that of Example 84.

mp : 74-78°C

IR (Nujol) : 1610, 1540 cm^{-1}

NMR (DMSO-d_6, δ) : 3.75 (3H, s), 3.79 (2H, s), 4.14 (2H, s), 6.34 (1H, d, J=2.8Hz), 6.98 (1H, d, J=7.3Hz), 7.13-7.94 (14H, m), 8.10-8.20 (1H, m), 8.41 (1H, s), 8.56 (1H, s)

MASS : 435 (M+1)

Example 90

N-(1-Methylindol-5-yl)-N'-[3-[(2,4,6-trimethoxybenzyl)-aminomethyl]phenyl]urea was prepared in a similar manner to that of Example 84.

mp : 144-152°C

IR (Nujol) : 1700, 1610, 1540 cm^{-1}

NMR (DMSO-d_6, δ) : 3.76 (3H, s), 3.79 (9H, s), 3.88

(2H, s), 3.96 (2H, s), 6.28 (2H, s), 6.33 (1H, d, J=2.8Hz), 7.05 (1H, d, J=7.7Hz), 7.16 (1H, d, J=8.6Hz), 7.28-7.40 (4H, m), 7.65 (1H, s), 7.71 (1H, s), 8.83 (1H, s), 8.99 (1H, s)

MASS : 475 (M+1)

Example 91

N-(1-Methylindol-5-yl)-N'-[3-[(2,4-dimethoxybenzyl)-aminomethyl]phenyl]urea was prepared in a similar manner to that of Example 84.

mp : 108-111°C

IR (Nujol) : 1610, 1600, 1580, 1540 cm^{-1}

NMR (DMSO-d_6, δ) : 3.66 (2H, s), 3.72 (2H, s), 3.75-3.77 (9H, m), 6.34 (1H, d, J=3.0Hz), 6.47-6.55 (2H, m), 6.94 (1H, d, J=7.4Hz), 7.12-7.38 (7H, m), 7.45 (1H, s), 7.70 (1H, d, J=1.6Hz), 8.52 (1H, s), 8.67 (1H, s)

MASS : 445 (M+1)

Example 92

N-[3-(1-Benzylaminoethyl)phenyl]-N'-(1-methylindol-5-yl)urea was prepared in a similar manner to that of Example 84.

mp : 75-90°C

IR (Nujol) : 1640 cm^{-1}

NMR (DMSO-d_6, δ) : 1.27 (3H, d, J=7Hz), 3.40-3.80 (3H, m), 3.76 (3H, s), 6.34 (1H, d, J=3Hz), 6.95 (1H, d, J=7Hz), 7.10-7.50 (12H), 7.69 (1H, d, J=2Hz), 8.39 (1H, s), 8.55 (1H, s)

Example 93

N-(Benzo[b]furan-5-yl)-N'-[3-(benzylaminomethyl)-phenyl]urea was prepared in a similar manner to that of Example 84.

mp : 130-131°C

IR (Nujol) : 1620, 3260 cm^{-1}

NMR (DMSO-d_6, δ) : 3.68 (2H, s), 3.72 (2H, s), 6.90-6.97 (2H, m), 7.18-7.51 (10H, m), 7.84 (1H, d, J=2.0Hz), 7.93 (1H, d, J=2.2Hz), 8.64-8.65 (2H, m)

MASS : 372 (M+1)

Example 94

N-(Benzo[b]furan-5-yl)-N'-[3-[(2,4,6-trimethoxybenzyl)-aminomethyl]phenyl]urea acetate was prepared in a similar manner to that of Example 84.

mp : 95-110°C

IR (Nujol) : 1660 cm^{-1}

NMR (DMSO-d_6, δ) : 3.78-3.89 (13H, m), 6.27 (1H, s), 6.90 (1H, s), 7.03 (1H, d, J=8.0Hz), 7.26-7.60 (5H, m), 7.84 (1H, s), 7.93 (1H, d, J=2.1Hz), 8.98 (1H, d, J=6.3Hz)

MASS : 462 (M+1)

Example 95

N-[3-[(3,4-Dimethoxybenzyl)aminomethyl]phenyl]-N'-(1-methylindol-5-yl)urea was prepared in a similar manner to that of Example 84.

mp : 100-110°C

IR (Nujol) : 1640 cm^{-1}

NMR (DMSO-d_6, δ) : 3.67 (3H, s), 3.73 (4H, s), 3.75 (6H, s), 6.33 (1H, d, J=2.9Hz), 6.88-7.00 (4H, m), 7.11-7.50 (6H, m), 7.68 (1H, s), 7.69 (1H, s), 8.45 (1H, s), 8.59 (1H, s)

MASS : 445 (M+1)

Example 96

N-(1-Methylindol-5-yl)-N'-[3-[(2,4,6-trimethylbenzyl)-aminomethyl]phenyl]urea was prepared in a similar manner to that of Example 84.

mp : 178-179°C

IR (Nujol) : 1635 cm^{-1}

NMR (DMSO-d_6, δ) : 2.18 (3H, s), 2.26 (6H, s), 3.58 (2H, s), 3.73 (2H, s), 3.75 (3H, s), 6.33 (1H, d, J=3.0Hz), 6.78 (2H, s), 6.96 (1H, d, J=7.4Hz), 7.11-7.45 (7H, m), 7.68 (1H, d, J=1.7Hz), 8.52 (1H, s), 8.58 (1H, s)

MASS : 427 (M+1)

Example 97

N-(Benzo[b]furan-5-yl)-N'-[3-[(2,4,6-trimethylbenzyl)-aminomethyl]phenyl]urea was prepared in a similar manner to that of Example 84.

mp : 183-185°C

IR (Nujol) : 1635 cm^{-1}

NMR (DMSO-d_6, δ) : 2.18 (3H, s), 2.26 (6H, s), 3.59 (2H, s), 3.75 (2H, s), 6.78 (2H, s), 6.90 (1H, t, J=0.86Hz), 6.99 (1H, d, J=7.5Hz), 7.18-7.52 (5H, m), 7.83 (1H, d, J=2.0Hz), 7.93 (1H, d, J=2.2Hz), 8.60 (1H, s), 8.63 (1H, s)

MASS : 414 (M+1)

Example 98

N-[3-[(3,4-Dihydroisoquinolin-1-yl)aminomethyl]phenyl]-N'-(1-methylindol-5-yl)urea hydroiodide was prepared in a similar manner to that of Example 66.

mp : 224-228°C

IR (Nujol) : 1600, 1630, 1675 cm^{-1}

NMR (DMSO-d_6, δ) : 3.03 (2H, t, J=6.4Hz), 3.54 (2H, t, J=6.7Hz), 3.75 (3H, s), 4.66 (2H, s), 6.33 (1H, d, J=2.9Hz), 6.97 (1H, d, J=7.1Hz), 7.13 (1H, dd, J=8.7Hz, 1.9Hz), 7.26-7.74 (9H, m), 8.06 (1H, d, J=7.7Hz), 8.46 (1H, s), 8.68 (1H, s), 9.90 (2H, s)

MASS : 424 (M+1)

Example 99

N-[3-[[(Methylimino)(phenyl)methyl]aminomethyl]phenyl]-N'-(1-methylindol-5-yl)urea was prepared in a similar manner to that of Example 66.

mp : 138-152°C

IR (Nujol) : 1640 cm^{-1}

NMR (DMSO-d_6, δ) : mixture of tautomers, [major, 3.07 (3H, s), 4.36 (2H, s)], [minor, 2.82 (2H, s), 4.62 (2H, s)], [both, 3.76 (3H, s), 6.34-6.35 (1H, m), 6.75-6.79 (1H, m), 7.00-7.68 (14H, m), 8.48-8.51 (1H, m), 8.64-8.71 (1H, m), 9.6-9.8 (1H, m)]

MASS : 412 (M+1)

Example 100

N-(Benzo[b]furan-7-yl)-N'-(3-cyanophenyl)urea was prepared in a similar manner to that of Example 1.

mp : 208-215°C (MeOH)

IR (Nujol) : 3300, 2240, 1640, 1610, 1560 cm^{-1}

NMR (DMSO-d_6, δ) : 7.00 (1H, d, J=2Hz), 7.19 (1H, t, J=8Hz), 7.31 (1H, d, J=7Hz), 7.48 (2H, m), 7.68 (1H, d, J=9Hz), 7.94 (1H, d, J=7Hz), 8.04 (2H, m), 8.99 (1H, s), 9.46 (1H, s)

Example 101

N-(Benzo[b]furan-7-yl)-N'-(3-thiocarbamoylphenyl)urea was prepared in a similar manner to that of Example 2.

mp : 155-164°C

IR (Nujol) : 3270, 1630, 1600, 1555 cm^{-1}

NMR (DMSO-d_6, δ) : 7.00 (1H, d, J=2Hz), 7.14-7.46 (4H, m), 7.75 (1H, m), 7.98-8.08 (2H, m), 8.60 (1H, s), 9.35 (1H, s), 9.51 (1H, s), 9.89 (1H, s)

Example 102

N-(Benzo[b]furan-7-yl)-N'-[3-[methylthio(imino)methyl]-phenyl]urea hydroiodide was prepared in a similar manner to that of Example 3.

mp : 180-182°C

IR (Nujol) : 3400, 3170, 1680, 1625, 1550 cm^{-1}

NMR (DMSO-d_6, δ) : 2.86 (3H, s), 7.00 (1H, d, J=2Hz), 7.20 (1H, t, J=8Hz), 7.32 (1H, d, J=7Hz), 7.46 (1H, d, J=8Hz), 7.60 (1H, t, J=8Hz), 7.70 (1H, d, J=8Hz), 7.94 (1H, d, J=8Hz), 8.08 (1H, d, J=2Hz), 8.20 (1H, m), 8.94 (2H, s), 9.56 (1H, s)

Example 103

N-(Benzo[b]furan-7-yl)-N'-[3-(phenylamidino)phenyl]urea was prepared in a similar manner to that of Example 6.

mp : 190-200°C

IR (Nujol) : 3200, 1675, 1650, 1625, 1590, 1540 cm^{-1}

NMR (DMSO-d_6, δ) : 7.01 (1H, d, J=2Hz), 7.19 (1H, t, J=8Hz), 7.32 (1H, d, J=7Hz), 7.40-7.80 (8H, m), 7.96 (1H, d, J=7Hz), 8.08 (1H, d, J=2Hz), 8.14 (2H, m), 9.00 (2H, m), 9.51 (1H, s)

Example 104

N-(1-Methylindol-5-yl)-N'-[3-[(2-thienylmethyl)-aminomethyl]phenyl]urea was prepared in a similar manner to that of Example 84.

Example 105

N-(1-Methylindol-5-yl)-N'-[3-[[(3-trifluoromethoxyphenyl)methyl]aminomethyl]phenyl]urea was prepared in a similar manner to that of Example 84.

Example 106

N-[3-[[(3-Methoxyphenyl)methyl]aminomethyl]phenyl]-N'-(1-methylindol-5-yl)urea was prepared in a similar manner to that of Example 84.

Example 107

N-[3-[[(2-Methoxy-5-trifluoromethoxyphenyl)methyl]-

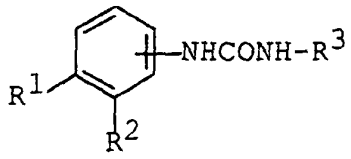
aminomethyl]phenyl]-N'-(1-methylindol-5-yl)urea was prepared in a similar manner to that of Example 84.

Example 108

N-(1-Methylindol-5-yl)-N'-[3-(phenethylaminomethyl)-phenyl]urea was prepared in a similar manner to that of Example 84.

C L A I M S

1. A compound of the formula :



wherein R^1 is cyano, thiocarbamoyl,
a group of the formula :

$$-(A^1\text{-}NH)_m\text{-}\overset{\overset{NH}{\|}}{C}\text{-}(NH)_n\text{-}R^4$$

in which R^4 is hydrogen, lower alkyl which may have optionally substituted aryl, acyl, optionally substituted aryl, lower alkylthio or 1-lower alkylindolyl,
A^1 is lower alkylene, and
m and n are each 0 or 1,
a group of the formula :

$$-A^2\text{-}R^5$$

in which R^5 is morpholino, piperidino, 4-arylpiperazin-1-yl, phthalimido, 1,2,3,4-tetrahydroquinolin-1-yl, 1,2,3,4-tetrahydroisoquinolin-2-yl or imidazol-1-yl, and
A^2 is lower alkylene, or
a group of the formula :

$$-A^3\text{-}\overset{\overset{R^6}{|}}{N}\text{-}R^7$$

in which R^6 and R^7 are each hydrogen, optionally substituted aryl, acyl, pyridyl(lower)alkyl, thienyl(lower)alkyl, 3,4-dihydroisoquinolinyl, (lower alkylimino)(optionally substituted aryl) methyl or lower alkyl which may have optionally substituted aryl, and

A^3 is lower alkylene, and

R^2 is hydrogen; or

R^1 and R^2 are linked together to form

$$-(CH_2)_3-\underset{\displaystyle R^8}{\underset{|}{CH}}- \ ,$$

$$-(CH_2)_2-\underset{\displaystyle R^9}{\underset{|}{N}}-CH_2- \ , \text{ or}$$

$$-(CH_2)_3-\underset{\displaystyle R^9}{\underset{|}{N}}- \ ,$$

in which R^8 is amino or acylamino, and

R^9 is hydrogen, acyl or lower alkyl which may have optionally substituted aryl, and

R^3 is 1-lower alkylindolyl, benzofuranyl, dihydrobenzofuranyl or optionally substituted aryl,

and a pharmaceutically acceptable salt thereof.

2. A compound of claim 1, wherein

R^1 is cyano, thiocarbamoyl,

a group of the formula :

$$-(A^1\text{-}NH)_m\text{-}\overset{\overset{NH}{\|}}{C}\text{-}(NH)_n\text{-}R^4$$

wherein R^4 is hydrogen, lower alkyl, phenyl(lower)alkyl, di(lower alkoxy)phenyl(lower)alkyl, phenyl(lower)alkoxycarbonyl, phenyl, lower alkoxyphenyl, lower alkylthio or 1-lower alkylindolyl,

A^1 is lower alkylene, and

m and n are each 0 or 1,

a group of the formula :

$$-A^2\text{-}R^5$$

wherein R^5 is morpholino, piperidino, 4-phenylpiperazin-1-yl, phthalimido, 1,2,3,4-tetrahydroquinolin-1-yl, 1,2,3,4-tetrahydroisoquinolin-2-yl or imidazol-1-yl, and

A^2 is lower alkylene, or

a group of the formula :

$$-A^3\text{-}\overset{\overset{R^6}{|}}{N}\text{-}R^7$$

wherein R^6 and R^7 are each hydrogen, phenyl, lower alkanoyl, phenyl(lower)alkoxycarbonyl, pyridyl(lower)alkyl, thienyl(lower)alkyl, 3,4-dihydroisoquinolinyl, (lower alkylimino)(phenyl)methyl, lower alkyl, phenyl(lower)alkyl, naphthyl(lower)alkyl, (mono- or di-

or trilower alkyl)phenyl(lower)-alkyl, (mono- or di- or trilower alkoxy)phenyl(lower)alkyl, (mono- or di- or trihalo)phenyl(lower)alkyl, [trihalo(lower)alkoxy]phenyl(lower)-alkyl or [lower alkoxy][trihalo-(lower)alkoxy]phenyl(lower)alkyl, and

A^3 is lower alkylene, and

R^2 is hydrogen; or

R^1 and R^2 are linked together to form

$$-(CH_2)_3-\underset{\displaystyle R^8}{\underset{|}{CH}}- \ ,$$

$$-(CH_2)_2-\underset{\displaystyle R^9}{\underset{|}{N}}-CH_2- \ , \text{ or}$$

$$-(CH_2)_3-\underset{\displaystyle R^9}{\underset{|}{N}}- \ ,$$

wherein R^8 is amino or lower alkanoylamino, and

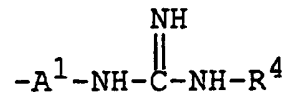
R^9 is hydrogen, phenyl(lower)alkoxycarbonyl or phenyl(lower)alkyl, and

R^3 is 1-lower alkylindolyl, benzofuranyl, dihydrobenzofuranyl or N,N-di(lower alkyl)aminophenyl.

3. A compound of claim 2, wherein

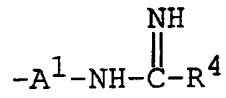
R^1 is cyano, thiocarbamoyl,

a group of the formula :



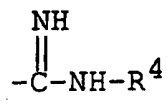
wherein R^4 is hydrogen or phenyl(lower)alkoxycarbonyl, and A^1 is lower alkylene,

a group of the formula :



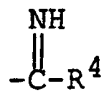
wherein R^4 is phenyl or 1-lower alkylindolyl, and A^1 is lower alkylene,

a group of the formula :



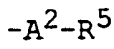
wherein R^4 is hydrogen, lower alkyl, phenyl(lower)alkyl, di(lower alkoxy)phenyl(lower)alkyl, phenyl or lower alkoxyphenyl,

a group of the formula :



wherein R^4 is lower alkylthio,

a group of the formula :

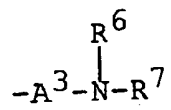


wherein R^5 is morpholino, piperidino,

4-phenylpiperazin-1-yl, phthalimido, 1,2,3,4-tetrahydroquinolin-1-yl, 1,2,3,4-tetrahydroisoquinolin-2-yl or imidazol-1-yl, and

A^2 is lower alkylene, or

a group of the formula :

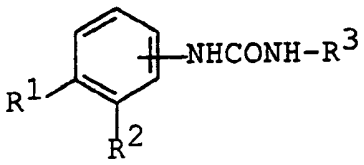


wherein R^6 and R^7 are each hydrogen, phenyl, lower alkanoyl, phenyl(lower)-alkoxycarbonyl, pyridyl(lower)alkyl, thienyl(lower)alkyl, 3,4-dihydroisoquinolinyl, (lower alkylimino)(phenyl)methyl, lower alkyl, phenyl(lower)alkyl, naphthyl(lower)alkyl, (mono- or di- or trilower alkyl)phenyl(lower)-alkyl, (mono- or di- or trilower alkoxy)phenyl(lower)alkyl, (mono- or di- or trihalo)phenyl(lower)alkyl, [trihalo(lower)alkoxy]phenyl(lower)-alkyl or [lower alkoxy][trihalo-(lower)alkoxy]phenyl(lower)alkyl, and

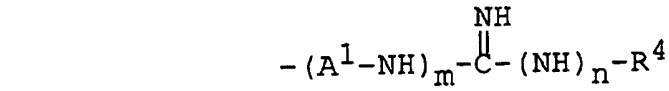
A^3 is lower alkylene, and

R^2 is hydrogen.

4. A process for preparing a compound of the formula :



wherein R^1 is cyano, thiocarbamoyl,
a group of the formula :



in which R^4 is hydrogen, lower alkyl which may have optionally substituted aryl, acyl, optionally substituted aryl, lower alkylthio or 1-lower alkylindolyl,
A^1 is lower alkylene, and
m and n are each 0 or 1,
a group of the formula :

in which R^5 is morpholino, piperidino, 4-arylpiperazin-1-yl, phthalimido, 1,2,3,4-tetrahydroquinolin-1-yl, 1,2,3,4-tetrahydroisoquinolin-2-yl or imidazol-1-yl, and
A^2 is lower alkylene, or
a group of the formula :

in which R^6 and R^7 are each hydrogen, optionally substituted aryl, acyl, pyridyl(lower)alkyl, thienyl(lower)alkyl,

3,4-dihydroisoquinolinyl, (lower alkylimino)(optionally substituted aryl) methyl or lower alkyl which may have optionally substituted aryl, and

A^3 is lower alkylene, and

R^2 is hydrogen; or

R^1 and R^2 are linked together to form

$$-(CH_2)_3-\underset{\displaystyle R^8}{CH}- \ ,$$

$$-(CH_2)_2-\underset{\displaystyle R^9}{N}-CH_2- \ , \text{ or}$$

$$-(CH_2)_3-\underset{\displaystyle R^9}{N}- \ ,$$

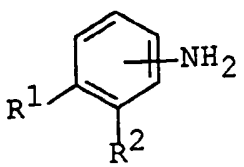
in which R^8 is amino or acylamino, and

R^9 is hydrogen, acyl or lower alkyl which may have optionally substituted aryl, and

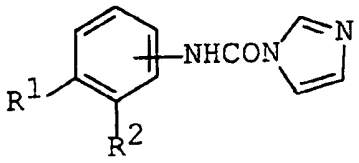
R^3 is 1-lower alkylindolyl, benzofuranyl, dihydrobenzofuranyl, or optionally substituted aryl,

or a pharmaceutically acceptable salt thereof, which comprises

(1) reacting a compound of the formula :



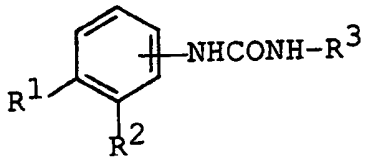
wherein R^1 and R^2 are each as defined above,
or a salt thereof,
with 1,1'-carbonyldiimidazole,
to give a compound of the formula :



wherein R^1 and R^2 are each as defined above,
or a salt thereof, and continuously reacting the obtained compound or a salt thereof, with a compound of the formula :

$$H_2N\text{-}R^3$$

wherein R^3 is as defined above,
or a salt thereof,
to give a compound of the formula :

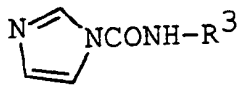


wherein R^1, R^2 and R^3 are each as defined above,
or a salt thereof, or

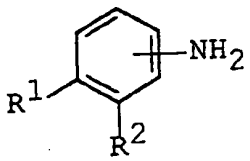
(2) reacting a compound of the formula :

$$H_2N\text{-}R^3$$

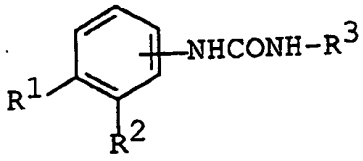
wherein R^3 is as defined above,
or a salt thereof,
with 1,1'-carbonyldiimidazole,
to give a compound of the formula :



wherein R^3 is as defined above,
or a salt thereof, and continuously reacting the obtained compound or a salt thereof, with a compound of the formula :

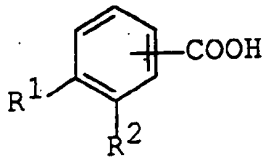


wherein R^1 and R^2 are each as defined above,
or a salt thereof,
to give a compound of the formula :

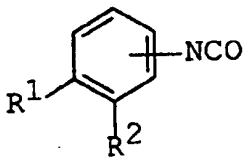


wherein R^1, R^2 and R^3 are each as defined above,
or a salt thereof, or

(3) subjecting a compound of the formula :



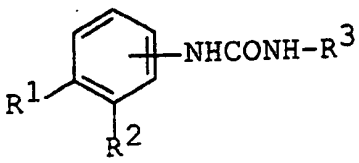
wherein R^1 and R^2 are each as defined above,
or a salt thereof,
to Curtius Rearrangement reaction,
to give a compound of the formula :



wherein R^1 and R^2 are each as defined above,
or a salt thereof, and continuously reacting the obtained compound or a salt thereof, with a compound of the formula :

$$H_2N\text{-}R^3$$

wherein R^3 is as defined above,
or a salt thereof,
to give a compound of the formula :



wherein R^1, R^2 and R^3 are each as defined above,
or a salt thereof, or

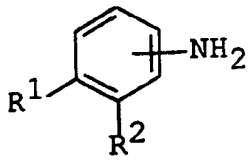
(4) subjecting a compound of the formula :

$$HOOC-R^3$$

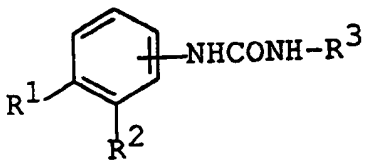
wherein R^3 is as defined above,
or a salt thereof,
to Curtius Rearrangement reaction,
to give a compound of the formula :

$$OCN-R^3$$

wherein R^3 is as defined above,
or a salt thereof, and continuously reacting the obtained compound or a salt thereof, with a compound of the formula :



wherein R^1 and R^2 are each as defined above,
or a salt thereof,
to give a compound of the formula :



wherein R^1, R^2 and R^3 are each as defined above, or a salt thereof.

5. A pharmaceutical composition which comprises a compound of claim 1 and a pharmaceutically acceptable carrier or excipient.

6. A process for preparing a pharmaceutical composition which comprises admixing a compound of claim 1 with a pharmaceutically acceptable carrier or excipient.

7. A compound of claim 1 for use as a medicament.

8. A compound of claim 1 for use as a 5-HT antagonist.

9. A compound of claim 1 for use as a 5-HT_{2C} antagonist.

10. A use of a compound of claim 1 for manufacturing a medicament for treating 5-HT mediated diseases.

11. A method for treating 5-HT mediated diseases which comprises administering a compound of claim 1 to human or animals.

INTERNATIONAL SEARCH REPORT

Internat ' Application No
PCT/JP 96/01500

A. CLASSIFICATION F SUBJECT MATTER
IPC 6 C07D209/08 A61K31/33 A61K31/17 C07D403/12 C07D401/12
C07D405/12 C07C327/48 C07C327/58 C07C275/58

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07D A61K C07C

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO,A,94 14801 (SMITHKLINE BEECHAM PLC) 7 July 1994 see claims	1,8,9
A	WO,A,93 18028 (SMITHKLINE BEECHAM PLC) 16 September 1993 see claims	1,8
A	WO,A,92 05170 (BEECHAM GROUP PLC) 2 April 1992 see claims; example 2	1,8
A	WO,A,95 06044 (SMITHKLINE BEECHAM PLC) 2 March 1995 see claims	18

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
13 September 1996	20.09.96

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax (+31-70) 340-3016	Van Bijlen, H

Form PCT/ISA/218 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/JP 96/01500

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
Although claim 11 is directed to a method of treatment of (diagnostic method practised on) the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searches without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

...rmation on patent family members

Internat 1 Application No
PCT/JP 96/01500

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
WO-A-9414801	07-07-94	NONE		
WO-A-9318028	16-09-93	EP-A-	0630373	28-12-94
		JP-T-	7504429	18-05-95
		US-A-	5508288	16-04-96
		ZA-A-	9301713	22-09-94
WO-A-9205170	02-04-92	AU-B-	642041	07-10-93
		AU-A-	8503891	15-04-92
		CA-A-	2091246	14-03-92
		EP-A-	0550507	14-07-93
		JP-T-	6500551	20-01-94
		US-A-	5328922	12-07-94
WO-A-9506044	02-03-95	EP-A-	0714389	05-06-96